

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
11 October 2001 (11.10.2001)

PCT

(10) International Publication Number
WO 01/75440 A2

(51) International Patent Classification⁷: **G01N 33/50**,
C12Q 1/68, C07K 14/47, C07H 21/04, C12N 15/63, C07K
16/18, A61K 31/7088, C12N 5/10, A01K 67/027

(21) International Application Number: PCT/GB01/01486

(22) International Filing Date: 2 April 2001 (02.04.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0007880.8 31 March 2000 (31.03.2000) GB
0012768.8 26 May 2000 (26.05.2000) GB

(71) Applicant (*for all designated States except US*):
WELFIDE CORPORATION [JP/JP]; 2-6-9, Hira-
nomachi, Chuo-ku, Osaka 541-0046 (JP).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **COCHRAN, Susan**
[GB/GB]; Welfide Corporation, 7-25. Koyata 3-Chome,
Iruma Saitama 358-0026 (JP). **PATERSON, Gary**
[GB/GB]; Yoshitomi Research Institute of Neuroscience in
Glasgow (YRING), West Medical Building, University of
Glasgow, Glasgow G12 8QQ (GB). **OHASHI, Yoshitaka**
[JP/JP]; Welfide Corporation, 7-25. Koyata 3-Chome,
Iruma Saitama 358-0026 (JP). **MORRIS, Brian** [GB/GB];
Yoshitomi Research Institute of Neuroscience in Glasgow
(YRING), West Medical Building, University of Glasgow,

Glasgow G12 8QQ (GB). **PRATT, Judith** [GB/GB];
Yoshitomi Research Institute of Neuroscience in Glasgow
(YRING), West Medical Building, University of Glasgow,
Glasgow G12 8QQ (GB).

(74) Agents: **MCCALLUM, William, Potter et al.**; Cruik-
shank & Fairweather, 19 Royal Exchange Square, Glasgow
G1 3AE (GB).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,
HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX,
MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL,
TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished
upon receipt of that report*

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: SCHIZOPHRENIA RELATED GENES

(57) Abstract: There are provided isolated polynucleotide fragments for use in diagnosing and/or developing treatments for schizophrenia. Further provided is a method for diagnosing schizophrenia using one or more polynucleotides disclosed herein. Also provided is a method for screening a compound which regulates expression of a schizophrenia-related gene. Also provided is a chronic animal model of schizophrenia that mimics the functional deficits observed in patients and methods for producing the animal model comprising the administration of PCP to the animal.

WO 01/75440 A2

SCHIZOPHRENIA RELATED GENES

The present invention relates to the identification of genes postulated to be involved and/or associated with schizophrenia. The present invention also relates to the development of a chronic animal model which mimics functional deficits in schizophrenia and to the use of the model in drug screening and identification of genes/proteins associated with schizophrenia, as well as particular identified genes and their use in therapy/diagnosis of schizophrenia.

Schizophrenia is a devastating mental illness which affects 1% of the world population, the aetiology of which remains elusive. To date, there is a poor understanding of the genes involved and no chronic animal models of schizophrenia have been developed which imitate all the characteristics of the disease.

One of the goals of modern antipsychotic drug development is to produce a drug which is more effective in ameliorating the negative symptoms and cognitive deficits characteristic of schizophrenia than existing therapies. Although typical and atypical antipsychotic drugs, such as haloperidol and clozapine, are effective in attenuating the positive symptoms, they are ineffective (haloperidol) or minimally effective (clozapine) against the negative symptoms and cognitive dysfunction associated with the disease (Goldberg, T. et al). The development of improved antipsychotic drugs which will have superior action against

the negative symptoms and cognitive dysfunction has been severely hampered by the lack of knowledge of which genes are involved and/or associated with schizophrenia, or lack of an animal model which accurately models these symptoms.

Many putative models of schizophrenia have been described to date. These range from developmental models (Lillrank et al), social isolation (Jones, G.H. et al) or social interaction (Sams-Dodd, F. et al) models to pharmacological models (Snyder, S.H. et al). The major drawbacks of the present pharmacological models of schizophrenia are that they are based on acute administration of the drugs. The models involve administering the drug to produce the psychotic state, but in order to test the activity of antipsychotic drugs, they are administered before the animal is exposed to amphetamine or Phencyclidine (PCP). This would be tantamount to administering an antipsychotic drug to a patient before the onset of schizophrenia. The models also do not account for the fact that antipsychotic treatment can take up to a month to have beneficial effects against the disease. Thus, the current models of schizophrenia fail to accurately mimic the clinical profile of the disease.

Moreover, little is known about the genes, or more specifically any alteration of expression/mutation of genes in a patient suffering from schizophrenia.

It is therefore amongst the objects of the present

invention to obviate and/or mitigate at least one of the aforementioned disadvantages.

The present invention is based in part on the development of a chronic animal model of schizophrenia using the drug phencyclidine (PCP) and the use of this model to identify genes thought to be involved and/or associated with schizophrenia. Although PCP has been known for many years to produce schizophrenic-like symptoms in man and also to worsen the psychotic state in schizophrenics (Allen, R.M. et al), it has hitherto not been used to develop a chronic animal model of schizophrenia that mimics the functional deficits observed in patients.

The present invention is also based in part on the elucidation of genes which are differentially expressed in the blood of schizophrenic patients.

Thus, according to a first aspect, there are provided isolated polynucleotide fragments for use in diagnosing and/or developing treatments for schizophrenia. The isolated polynucleotide fragments are shown in the attached Figures 1, 2, 3, 4, 5a, 6a, 6c, 6e, 7a, 8a, 9a, 9c and 10a. The inventors have presently identified 10 genes which have been observed to be differentially expressed in the animal model disclosed herein or in blood samples from schizophrenic patients. The genes have been designated YSG1-10. The YSG3 (Figure 1: SEQ ID No. 1), YSG4 (Figure 2: SEQ ID No. 2), YSG6 (Figure 3: SEQ ID No. 3) and YSG9

(Figure 4: SEQ ID No. 4) are shown to be novel sequences based on database screening. The remaining sequences are known genes not however previously being associated with schizophrenia; YSG1 (Figure 5a: SEQ ID No. 5) relates to phosphodiesterase 1 α ; YSG2 (Figures 6a, 6c, 6e: SEQ ID Nos. 7, 9 & 11, respectively) relates to calcium-independent alpha-latrotoxin receptor (CIRL 1, 2 & 3); YSG5 (Figure 7a: SEQ ID No. 13) relates to epithelial discoidin domain receptor 1, trkE; YSG7 (Figure 8a: SEQ ID No. 15) relates to netrin receptor UNC5H1; YSG8 (Figures 9a, 9c: SEQ ID Nos. 17 & 19, respectively) relates to synapsins 1A and 1B; and YSG10 (Figure 10a: SEQ ID No. 21) relates to TNF α .

Thus the present invention provides a polynucleotide having DNA sequence represented by SEQ ID No. 1; a polynucleotide having DNA sequence represented by SEQ ID No. 2; a polynucleotide having DNA sequence represented by SEQ ID No. 3; or a polynucleotide having DNA sequence represented by SEQ ID No. 4.

The present invention also provides a method for diagnosing schizophrenia which comprises using one or more polynucleotides selected from the group consisting of SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5 (PDE1 α), SEQ ID No. 7, 9 & 11 (CIRL 1, 2 & 3), SEQ ID No. 13 (trkE), SEQ ID No. 15 (netrin receptor), SEQ ID No. 17 & 19 (synapsin 1A/1B) and SEQ ID No. 21 (TNF α) as indicator(s).

The above described polynucleotide fragments have been

discovered to be differentially expressed in a chronic animal model as described herein or in the blood of schizophrenic patients and are postulated therefore to be putatively involved and/or associated with schizophrenia.

"Polynucleotide fragment" as used herein refers to a polymeric form of nucleotides of any length, both to ribonucleic acid sequences and to deoxyribonucleic acid sequences. In principle, this term refers to the primary structure of the molecule. Thus, the term includes double stranded and single stranded DNA, as well as double and single stranded RNA, and modifications thereof.

In a further aspect the present invention provides polynucleotide fragments encoding polypeptides for use in diagnosing and/or developing treatments for schizophrenia.

In particular the polypeptides are shown in Figures 5b, 6b, 6d, 6f, 7b, 8b, 9b, 9d and 10b, relating to SEQ ID Nos. 6, 8, 10, 12, 14, 16, 18, 20 & 22.

In general, the term "polypeptide" refers to a molecular chain of amino acids with a biological activity. It does not refer to a specific length of the product, and if required can be modified in vivo and/or in vitro, for example by glycosylation, myristoylation, amidation, carboxylation or phosphorylation; thus inter alia peptides, oligopeptides and proteins are included. The polypeptides disclosed herein may be obtained by synthetic or recombinant techniques known in the art.

Thus, the term extends to cover for example

polypeptides obtainable from various transcripts and splice variants of these transcripts from a particular gene.

It will be understood that for the polynucleotide fragments and polypeptide sequences presented herein, natural variations can exist between individuals. These variations may be demonstrated by nucleotide and/or amino acid differences in the overall sequence or by deletions, substitutions, insertions or inversions of nucleotides or amino acids in said sequences.

As is well known in the art, the degeneracy of the genetic code permits substitution of bases in a codon resulting in another codon for the same amino acid. Consequently, it is clear that any such derivative nucleotide sequence based on the sequences disclosed herein are also included in the scope of the present invention.

Thus, the present invention further includes nucleotide and/or polypeptide sequences having at least 80%, particularly at least 90%, and especially at least 95% homology or similarity with the sequences shown in the attached Figures.

The present invention also includes nucleotide sequences similar to the polynucleotide sequences disclosed herein. It is understood that similar sequences include sequences which remain hybridised to the polynucleotide sequences of the present invention under stringent conditions. Typically a test similar sequence and a polynucleotide sequence of the present invention are

allowed to hybridise for a specified period of time generally at a temperature of between 50 and 70°C in double strength SSC (2 x NaCl 17.5g/l and sodium citrate (SC) at 8.8 g/l) buffered saline containing 0.1% sodium dodecyl sulphate (SDS) followed by rinsing of the support at the same temperature but with a buffer having a reduced SSC concentration. Depending upon the degree of similarity of the sequences, such reduced concentration buffers are typically single strength SSC containing 0.1% SDS, half strength SSC containing 0.1% SDS and one tenth strength SSC containing 0.1% SDS. Sequences having the greatest degree of similarity are those the hybridisation of which is least affected by washing in buffers of reduced concentration.

It is most preferred that the similar and inventive sequences are so familiar that the hybridisation between them is substantially unaffected by washing or incubation in one tenth strength SSC containing 0.1% SDS.

Furthermore, fragments derived from the polynucleotide fragments depicted in the Figures may be used.

Moreover, fragments derived from the encoded polypeptides are also encompassed by the present invention.

All such modifications mentioned above resulting in such derivatives of the polypeptides are covered by the present invention so long as the characteristic polypeptide properties remain substantially unaffected in essence.

The information presented herein can be used to genetically manipulate the sequences or derivatives

thereof, for example to clone the sequences by recombinant DNA techniques generally known in the art. Cloning of homologous sequences from other species of mammal, and in particular humans, may be performed with the information disclosed herein by widely known techniques; for example, oligonucleotides may be designed to a consensus region and/or functional domains of the sequences shown in the Figures and such oligonucleotides, and/or the polymerase chain reaction products generated using these oligonucleotide primers, can be used as probes for cloning homologous sequences from other organisms, for example by polymerase chain reaction or by hybridisation.

The polynucleotide fragments of the present invention may be linked to expression control sequences. Such control sequences may comprise promoters, operators, inducers, ribosome binding sites etc. Suitable control sequences for a given host may be selected by those of ordinary skill in the art.

A nucleotide sequence according to the present invention can be ligated to various expression-controlling DNA sequences, resulting in a so-called recombinant nucleic acid molecule. Thus the present invention also includes an expression vector comprising an expressible nucleotide sequence. Said recombinant nucleic acid molecule can then be used for transformation of a suitable host.

Such recombinant nucleic acid molecules are preferably derived from for example, plasmids, or from nucleic acid

sequences present in bacteriophages or viruses and are termed vector molecules.

Specific vectors which can be used to clone nucleotide sequences according to the invention are known in the art (eg. Rodriguez RL and DT Denhardt, editors, Vectors: A survey of molecular cloning vectors and their uses, Butterworths, 1988).

The methods to be used for the construction of a recombinant nucleic acid molecule according to the invention are known to those of ordinary skill in the art and are inter alia set forth in Sambrook et al, Molecular Cloning: A Laboratory Manual, Cold Spring Harbour Laboratory, 1989.

The present invention also relates to a transformed cell comprising the polynucleotide fragments of the present invention, in expressible form, if appropriate. "Transformation", as used herein, refers to the introduction of a heterologous nucleic acid sequence into a host cell *in vivo*, *ex vivo* or *in vitro* irrespective of the method used, for example, by calcium phosphate co-precipitation, direct uptake, electroporation or transduction.

The heterologous nucleic acid sequence may be maintained through autonomous replication or alternatively may be integrated into the host's genome. The recombinant DNA molecules preferably are provided with appropriate control sequences, compatible with the designated host

which can regulate the expression of the inserted nucleic acid sequence.

The most widely used hosts for expression of recombinant nucleic acid molecules are bacteria, yeast, insect cells and mammalian cells. Each system has advantages and disadvantages in terms of the vector used, potential ease of production and purification of a recombinant polypeptide and authenticity of product in terms of tertiary structure, glycosylation state, biological activity and stability and will be a matter of choice for the skilled addressee.

In addition to expressing the polynucleotide fragments of the present invention, in certain circumstances, it is advantageous to substantially prevent or reduce the expression or activity of the polynucleotide fragments in a cell or host. Thus, according to a further aspect of the invention, there is provided an antisense nucleotide fragment complementary to a polynucleotide fragment or subfragment of the present invention. Included in the scope of "antisense nucleotide fragment" is the use of synthetic oligonucleotide sequences, or of equivalent chemical entities known to those skilled in the art, for example, peptide nucleic acids. Also provided is a nucleotide fragment comprising a nucleotide sequence which, when transcribed by the cell, produces such an antisense fragment. Typically antisense RNA fragments will be provided which bind to complementary mRNA fragments to form

RNA double helices, allowing RNase H to cleave the molecule and rendering it incapable of being translated by the cell into polypeptides.

A further aspect of the present invention provides antibodies specific to the polypeptides of the present invention or epitopes thereof. Production and purification of antibodies specific to an antigen is a matter of ordinary skill, and the methods to be used are clear to those skilled in the art. The term antibodies can include, but is not limited to polyclonal antibodies, monoclonal antibodies (mAbs), humanised or chimeric antibodies, single chain antibodies, Fab fragments, $F(ab')_2$ fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies, and epitope binding fragments of any of the above. Such antibodies may be used in modulating the expression or activity of the particular polypeptide, or in detecting said polypeptide in vivo or in vitro.

The present invention further provides a recombinant or synthetic polypeptide for the manufacture of reagents for use as therapeutic agents in the treatment of schizophrenia. In particular, the invention provides pharmaceutical compositions comprising the recombinant or synthetic polypeptide together with a pharmaceutically acceptable carrier therefor.

The present invention also relates to methods for prognostic and/or diagnostic evaluation of schizophrenia

and/or for the identification of subjects who are predisposed to schizophrenia, for example by examination of allelic variation by determination of the expression or sequence of the genes identified herein in an individual. Furthermore, the invention provides methods for evaluating the efficacy of drugs for such disorders, and monitoring the progress of patients involved in clinical trials for the treatment of such disorders.

Thus the invention further provides methods for the identification of compounds which modulate the expression of the polynucleotide fragments and/or the activity of polypeptide sequences identified herein. Such identified compounds may be used in the treatment of schizophrenia.

Thus there is provided a method for screening a compound which regulates expression of a schizophrenia-related gene(s), which comprises:

(a) bringing a test compound into contact with transformed cell which enables expression of a gene selected from the group consisting of SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5 (PDEI α), SEQ ID No. 7, 9 & 11 (CIRL 1, 2 & 3), SEQ ID No. 13 (trkE), SEQ ID No. 15 (netrin receptor), SEQ ID No. 17 & 19 (Synapsin 1A/AB) and SEQ ID No. 21 (TNF α),

(b) detecting an expression of schizophrenia-relating factor in said cell, and

(c) selecting a compound which promotes or suppresses an induction of the schizophrenia-relating factor in

comparison with a control (vehicle).

There is also provided a method for measuring an anti-schizophrenic effects of a compound using the animal model of the present invention, which comprises:

(a) measuring local cerebral glucose utilisation (LCGU), or detecting an expression level of one or more genes represented by the group consisting of SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5 (PDE 1 α), SEQ ID No. 7, 9 & 11 (CIRL 1, 2 & 3), SEQ ID No. 13 (trkE), SEQ ID No. 15 (netrin receptor), SEQ ID No. 17 & 19 (synapsin 1A/1B) and SEQ ID No. 21 (TNF α), and

(b) comparing with a control group.

The biological function of the genes identified herein can be more directly assessed by utilizing relevant *in vivo* and *in vitro* systems. *In vivo* systems can include, but are not limited to, animal systems which naturally exhibit the symptoms of schizophrenia, or ones which have been engineered to exhibit such symptoms, as for example the model described herein. Further, such systems can include, but are not limited to transgenic animal systems. *In vivo* systems can include, but are not limited to, cell-based systems comprising the identified gene/polypeptide expressing cell types. The cells can be wild type cells, or can be non-wild type cells containing modifications known or suspected of contributing to schizophrenia.

In further characterising the biological function of said identified gene(s), the expression of said identified

gene(s) can be modulated within the *in vivo* and/or *in vitro* systems, i.e. either overexpressed or underexpressed in, for example, transgenic animals and/or cell lines, and its subsequent effect on the system can then be assayed. Alternatively, the activity of the product of the identified gene can be modulated by either increasing or decreasing the level of activity in the *in vivo* and/or *in vitro* system of interest, and its subsequent effect then assayed.

The information obtained through such characterisations can suggest relevant methods for the treatment or control of schizophrenia. For example, relevant treatment can include a modulation of gene expression and/or gene product activity. Characterisation procedures such as those described herein can indicate whether such modulation should be positive or negative. As used herein, "positive modulation" refers to an increase in gene expression or activity of the gene or gene product of interest. "Negative modulation", as used herein, refers to a decrease in gene expression or activity.

In vitro systems can be designed to identify compounds capable of binding said identified gene(s) products of the invention. Compounds identified can be useful, for example, in modulating the activity of wild type and/or mutant gene(s) products, can be useful in elaborating the biological function of said identified gene(s) products, or

can disrupt normal identified gene(s) product interactions.

In another aspect the present invention provides a chronic animal model of schizophrenia that mimics the functional deficits observed in patients wherein the animal model has been developed by the addition of PCP to an animal.

In a further aspect the present invention provides a method for developing a chronic animal model of schizophrenia, said method comprising the steps of:

a) administering PCP to an animal in order to induce a psychotic state in the animal representative of the onset of schizophrenia in humans; and

b) further administering of PCP in order to maintain the PCP-induced psychotic state in the animal, over a period of time, to mimic a chronic state of schizophrenia in the animal.

The present invention also relates to an animal model produced by the method(s) of the present invention.

The animals of the present invention may be any suitable non-human animal. Typically the animal is a rat, mouse, guinea pig, rabbit or the like.

As mentioned above the present invention relates to the development of a chronic animal model. It is understood that the term chronic relates to a disease which is deep-seated or long-continued as opposed to an acute or rapidly developed disease.

The present inventors have developed a chronic

treatment paradigm which comprises two phases. The initial phase involves a period of treatment with PCP which was hypothesised would induce a psychotic state within the animal such as a rat, representing the onset of the disease in humans. The second phase concerns the maintenance of this PCP-induced psychotic state over a time period which would allow the incorporation of chronic antipsychotic therapy, relating to the therapeutic delay in antipsychotic efficacy observed in humans. The observation of a psychotic state may be measured in a number of ways. However, the measurement of the "psychotic state" was determined by the present inventors as PCP-induced hypofrontality which is observed in similar human imaging studies and is correlated to the negative symptoms and cognitive dysfunction associated with chronic schizophrenia (Wolkin, A. et al).

The initial administration of PCP to animal must be sufficient to induce a psychotic state and further administration of PCP must be sufficient to maintain the PCP-induced psychotic state. The present inventors have observed that an initial amount of PCP required to induce a psychotic state may be insufficient to maintain and mimic a chronic state of schizophrenia in the animal.

It has been previously observed that a level of 0.86 mgkg⁻¹ is sufficient to induce an acute state of schizophrenia in an animal model, but the present inventors have found that this is insufficient to maintain and induce

a chronic state. The present inventors have used a level of 2.58 mgkg^{-1} to maintain and induce a chronic state of schizophrenia in a rat model. Thus, the present invention provides a method for developing a chronic animal model of schizophrenia which includes administering a level of 1 to 5 mgkg^{-1} PCP, for example, a level of 2 to 4 mgkg^{-1} , such as, a level of 2.58 mgkg^{-1} to an animal to induce a chronic state of schizophrenia.

The effects of this PCP treatment paradigm on dopamine utilisation within selected brain areas was also investigated by HPLC analysis. The levels of dopamine metabolites within plasma and CSF of schizophrenic patients has been established and it has been found that chronic schizophrenics have lower levels of both homovanillic acid (HVA) and dihydroxyphenylacetic acid (DOPAC) compared to controls (Heritch, A.J). This implies that there is decreased turnover of dopamine within the schizophrenic brain.

For a working animal model of a disease to be valid there are certain underlying criteria which are fundamental and which must be taken into consideration. The first criteria, construct validity, is defined as the ability of the model to mimic the underlying neurobiological abnormalities which are core characteristics of the disease. This is difficult to emulate for schizophrenia, since the aetiology of the disease is far from clear. The second criteria, face validity, is defined as the model

must produce symptomatologies that resemble those characteristically observed in the disease. The third criteria, predictive validity, is defined as drugs which have established action against a disease must restore parameters in the animal model to normal, whereas other classes of drugs should be inactive.

The chronic PCP model described here satisfies these criteria to an impressive degree. The model uses a drug which is known to produce effects in humans which are analogous to those observed in schizophrenia.

Although the psychotic state may not be triggered by the same mechanism it is likely, from the evidence produced, that the psychosis is being mediated by the same systems which are implicated in the dysfunction associated with schizophrenia, such as the glutamatergic (Tamminga, C.) and dopaminergic (Angrist, B. et al) systems. The model also shows altered function in specific neural circuits, the corticothalamic and temporolimbic circuits, which have been shown to be abnormal in schizophrenia (Swerdlow, N.R. et al and Weinberger, D.R). The model also has face validity, with metabolic hypofunction, and changes in receptor binding being observed with this model and in schizophrenia. The predictive validity of the model is more difficult to evaluate, although the lack of reversibility of the prefrontal cortex hypofunction mirrors the clinical observations. However, the attenuation of the hypofunction within the auditory system by known

antipsychotic drugs suggest that this model does have predictive validity.

The model was also studied for parvalbumin expression which has been shown to be decreased in post mortem tissue of schizophrenic subjects. Parvalbumin expression in the model was also reduced in the prefrontal cortex, as observed in schizophrenic subjects. The model thus reproduces an established pattern of brain dysfunction associated with schizophrenia. This observation may have utility in developing novel antipsychotic drugs.

The model finds particular application in the screening of new drugs for treating schizophrenia. Thus, test drugs may be administered to the animal model and their effect on psychotic conditions observed. The present invention therefore also relates to new anti-schizophrenic drugs identified using the animal model of the present invention.

The model also allows the detection of genes, the expression of which is altered, as compared to a "normal" animal. A "normal" animal is one which has not been induced to the chronic psychotic state and which exhibits normal behaviours.

Genes identified in this manner may be associated with the schizophrenic state. Therefore identification of such genes allows their study and/or development of therapies designed to return expression to normal.

The present invention will now be further described by

way of non-limiting example and with reference to the attached Figures (where CLO indicated clozapine and HAL indicates haloperidol) which show:

Figures 1 - 4 show the nucleotide sequence of four sequences observed to be differentially expressed in the brain of the rat model of the present invention;

Figure 5a shows the nucleotide sequence and Figure 5b shows the polypeptide sequence of phosphodiesterase 1 α which have been observed to be differentially expressed in the brain of the rat model of the present invention;

Figures 6a, 6c and 6e show the nucleotide sequences and Figures 6b, 6d and 6f show the polypeptide sequences of calcium-independent alpha-latrotoxin receptor which have been observed to be differentially expressed in the brain of the rat model of the present invention;

Figure 7a shows the nucleotide sequence and Figure 7b shows the polypeptide sequence of epithelial discoidin domain receptor, trkE, which has been observed to be differentially expressed in the blood of schizophrenic patients as compared to normal controls;

Figure 8a shows the nucleotide sequence and Figure 8b shows the polypeptide sequence of netrin receptor which has been observed to be differentially expressed in the brain of the rat model of the present invention;

Figures 9a and 9c show the nucleotide sequence and Figures 9b and 9d show the polypeptide sequence of synapsins 1A and 1B which have been observed to be

differentially expressed in the brain of the rat model of the present invention;

Figure 10a shows the nucleotide sequence and Figure 10b shows the polypeptide sequence of YSG9 (Seq ID No. 19) which has been observed to be differentially expressed in the brains of schizophrenic patients and PCP-treated rats as compared to normal controls;

Figure 11 is a histogram showing the relative expression levels of genes in human blood samples;

Figure 12 shows parvalbumin expression in brain tissue of the animal model of the present invention;

Figure 13 illustrates the level of CIRL1 mRNA present in the BA11 region of schizophrenic (grey dashed line, n=6) and control (black, n=8) post-mortem tissue. TCTCCTGGCTGTGCCTGGAGGGC and GGCTTGAGCACAGATCAGCTTCGG were the primer sequences used to amplify this product.

Figure 14 illustrates the level of CIRL1 mRNA present in the prefrontal cortex of rat brain following chronic PCP and antipsychotic treatment (n=12 for all groups apart from veh-veh where n=11). TCTCCTGGCTGTGCCTAGAGGGC and GGCTTGAGCACGGATGAGCTTCGG were the primer sequences used to amplify this product.

Figure 15 illustrates the level of CIRL2 variant AB mRNA present in the prefrontal cortex of rat brain following chronic PCP and antipsychotic treatment (n=12 for all groups apart from veh-veh where n=11). GGAAAACATTAAGTCTTGGGTG and GTGAATGTCCTTGATTAAGGGT were the

primer sequences used to amplify this product.

Figure 15 illustrates the level of CIRL3 variant AA mRNA present in the prefrontal cortex of rat brain following chronic PCP and antipsychotic treatment (n=12 for all groups apart from veh-veh where n=11). GTAGTTCATGCTTTCAGCCGT and AGAAGCCCCTCTCTGTTGAG were the primer sequences used to amplify this product.

Figure 17 illustrates the expression profile of TNF α 2 and 24hrs after a single i.p. injection of PCP at 2mg/kg (N=4 for all treatment groups). AGGAGGAGAAGTTCCCAAATG and TTGTCCCTTGAAGAGAACCTG were the primer sequences used to amplify this product.

Figure 18 illustrates the levels of TNF α in rat prefrontal cortex following chronic PCP and antipsychotic treatment (n=12 for all groups apart from veh-veh where n=11). AGGAGGAGAAGTTCCCAAATG and TTGTCCCTTGAAGAGAACCTG were the primer sequences used to amplify this product.

Figure 19 illustrates the levels of TNF α in postmortem orbital frontal cortex of schizophrenics (n=4) and controls (n=5). GGTAGGAGACGGCGATGC and CAGGCAGTCAGATCATCTTC were the primer sequences used to amplify this product.

Example 1 - Development of rat model

An initial treatment period of intraperitoneal (i.p.) injections once daily for 5 days was carried out, followed by a maintenance schedule of i.p. injections three times weekly (every 60 hours) for a further 21 days.

Intermittent exposure to PCP during the maintenance phase of the model was favoured due to the long half life of the drug within brain tissue (Misra, A.L. et al). The doses of PCP chosen represented the selective blockade of the NMDA channel (0.86 mgkg^{-1}) and a dose (2.58 mgkg^{-1}) which is pharmacologically less selective but less than the ED_{50} for PCP-induced cell death. As a comparison to the present model, the inventors also investigated the effect of previously published subchronic treatment with PCP (Jentsch, J.D. et al) using quantitative C-2-deoxyglucose autoradiography (Sokoloff, L.).

Local cerebral glucose utilisation (LCGU) was measured using an adaptation of the original method for freely moving rats (Crane, A.M. et al) 72 hours after the initial induction phase (day 8) and 72 hours after the induction phase followed by the maintenance phase (day 29). LCGU was measured 72 hours after the last exposure to PCP so the effects of PCP on LCGU would be independent of the acute effects of the drug. Table 1 shows the results from the induction and maintenance phases of the model. The dose of 2.58 mgkg^{-1} PCP induced a metabolic hypofunction which was evident after both phases of the model within the medial orbital cortex, the prelimbic cortex, the auditory pathway and the reticular nucleus of the thalamus. The metabolic hypofunction produced by the lower dose of PCP (0.86 mgkg^{-1}) within these areas during the initial phase of the model

was not, however, maintained by the subsequent second phase of the model. Thus, using a dose of 2.59 mgkg^{-1} the inventors had established a novel treatment paradigm which mimics the findings of human imaging studies in schizophrenic patients. In comparison, the previously published subchronic treatment (Jentsch et al) with PCP (5 mgkg^{-1} twice daily for seven days) did not produce any significant effect on LCGU within any brain area (data not shown).

In summary, the data provided from the animal studies utilising this chronic PCP model mimic those previously published from human imaging studies and post mortem studies of schizophrenic brain tissue from schizophrenic patients. Since human imaging studies have correlated the prefrontal hypofunction to the negative symptoms of schizophrenia (Wolkin, A. et al, 1992) and abnormalities of the temperolimbic system (including the auditory system and hippocampus) and thalamus to the positive symptoms of schizophrenia (Tamminga, C.A. et al, 1992), it can be proposed that this model mimics both the positive and negative symptoms of the disease. As such, this model has superior construct, face and predictive validity than existing animal models of schizophrenia.

Table 1: Induction and maintenance of PCP-induced hypofunction

		LCGU ($\mu\text{mol}/100\text{g}/\text{min}$)				
		day 8	2.58		day 29	2.58
		0.86	PCP	vehicle	0.86	PCP
		PCP			PCP	
<i>Prefrontal Cortex</i>						
mO layer	131 \pm 4	110 \pm 2*	105 \pm 4*	125 \pm 4	122 \pm 3	108 \pm 5*
mO layers II & III	137 \pm 4	127 \pm 2	127 \pm 5	147 \pm 3	135 \pm 4	124 \pm 5
mO layers V & VI	140 \pm 1	129 \pm 5*	115 \pm 1*	137 \pm 2	136 \pm 3	111 \pm 3*
PrL layer I	134 \pm 2	132 \pm 6	104 \pm 2*	135 \pm 1	133 \pm 2	107 \pm 4*
PrL layers II & III	154 \pm 3	150 \pm 7	133 \pm 2*	152 \pm 2	149 \pm 2	116 \pm 1*
PrL layers V & VI	114 \pm 3	115 \pm 3	96 \pm 3*	114 \pm 2	112 \pm 3	89 \pm 2*
<i>Thalamus</i>						
Rt	116 \pm 2	106 \pm 2	86 \pm 2*	118 \pm 4	108 \pm 4	89 \pm 2*
MD	114 \pm 4	112 \pm 4	115 \pm 4	121 \pm 6	122 \pm 5	116 \pm 3

		LCGU ($\mu\text{mol}/100\text{g}/\text{min}$)				
		day 8	2.58		day 29	2.58
		0.86	PCP	vehicle	0.86	PCP
		PCP			PCP	
<i>Auditory System</i>						
Au layer I	159 \pm 11	127 \pm 2	135 \pm 3*	158 \pm 13	167 \pm 14	137 \pm 5*
Au layers II, III & IV	171 \pm 13	152 \pm 3	166 \pm 5	184 \pm 8	189 \pm 12	162 \pm 6
Au layers V & VI	122 \pm 8	114 \pm 4	120 \pm 4	128 \pm 9	137 \pm 10	115 \pm 3
AuD layer I	155 \pm 12	126 \pm 3*	135 \pm 3*	167 \pm 9	159 \pm 11	130 \pm 7*
AuD layers II, III & IV	178 \pm 14	151 \pm 4*	151 \pm 4*	189 \pm 9	178 \pm 10	146 \pm 7*
AuD layers V & VI	127 \pm 7	106 \pm 2*	104 \pm 2*	133 \pm 7	128 \pm 9	101 \pm 4*
DLL	116 \pm 7	91 \pm 4*	83 \pm 4*	118 \pm 7	116 \pm 8	96 \pm 5*
VLL	125 \pm 9	98 \pm 5*	93 \pm 3*	121 \pm 6	118 \pm 13	99 \pm 4*
cochlear nucleus	126 \pm 4	107 \pm 3*	98 \pm 3*	124 \pm 3	117 \pm 2	94 \pm 4*

Table 1: All data expressed as mean LCGU ($\mu\text{mol}/100\text{g}/\text{min}$) \pm SEM (n=5-6). Statistical analysis carried out using individual one-way ANOVA for each discrete brain region followed by Fisher's least significant difference post hoc test where appropriate, with statistical significance defined as $p < 0.05$. * $p < 0.05$ compared to controls. Day 8 data represents LCGU measured 72 hours

following the last exposure to PCP after 5 days i.p. injections once daily of 0.86 or 2.58 mgkg⁻¹ PCP or vehicle (sterile saline). Day 29 data represents LCGU measured 72 hours following the last exposure to PCP after i.p. injections once daily (day 1-5) and once daily on days 8, 10, 12, 15, 17, 19, 22, 24 and 26 of 0.86 or 2.58 mgkg⁻¹ PCP or vehicle (sterile saline).

Abbreviations: mO, medial orbital cortex; PrL, prelimbic cortex; Rt reticular nucleus of the thalamus; MD, mediodorsal nucleus of the thalamus; Au, primary auditory cortex; AuD, dorsal nucleus of the secondary auditory cortex; DLL & VLL, dorsal nucleus and ventral nucleus of the lateral lemniscus.

Example 2 - Testing of rat model

In order to establish the effect of antipsychotic drugs in the model, a second study was then carried out using a dose of 2.58 mgkg⁻¹ PCP which produced a metabolic hypofunction in the first studies, combined with antipsychotic therapy. The antipsychotic drugs were administered via osmotic minipumps for 21 days in order to maintain constant plasma concentrations of the drugs, which mirrored therapeutic plasma levels of the drugs in humans.

Table 2 shows the effect of haloperidol and clozapine alone and in conjunction with PCP treatment compared to

vehicle treated rats. Within the medial orbital cortex, the prelimbic cortex, the CA1 region of the hippocampus and the reticular nucleus of the thalamus, a metabolic hypofunction was again observed after treatment with PCP compared to controls. Clozapine and haloperidol also produced a metabolic hypofunction within these areas and failed to modulate the hypofunction produced by PCP. Within the auditory system, the dorsal nucleus of the secondary auditory cortex, dorsal and lateral nucleus of the lateral lemniscus and the cochlear nucleus, PCP again induced a metabolic hypofunction. However, within these regions, clozapine and haloperidol did not produce a significant hypofunction by themselves, but reversed the PCP-induced hypofunction when used in conjunction with the PCP. The inability of haloperidol and clozapine to modulate the hypofrontality is consistent with data from clinical studies and also the theory that this hypofrontality is associated with the negative symptoms and cognitive dysfunction of schizophrenia. The effect of antipsychotics on the positive symptoms is less well studied regarding imaging studies. There is no published evidence to date regarding the effect of haloperidol and clozapine within the temporal lobe structures (hippocampus and auditory cortex).

However, the ability of both antipsychotics to reverse the decreased glucose utilisation within the auditory system (auditory cortex, lateral lemniscus and the cochlear

nucleus) is consistent with the clinical evidence that both typical and atypical antipsychotics can improve ratings of positive symptoms of schizophrenia.

In order to further validate this chronic PCP model, the effects of this treatment paradigm on 5-HT_{2A} receptors within the prefrontal cortex was investigated. Chronic PCP treatment produced a significant decrease in 5-HT_{2A} receptors in layer II & III (controls 158±6, PCP 139±4 fmolmg⁻¹) and layers V & VI (controls 82 ±4, PCP 69±3 fmolmg⁻¹). This is entirely consistent with post mortem studies of 5-HT_{2A} receptor binding from schizophrenic patients (Laurelle, M. et al).

In order to validate further this chronic PCP model the effect of this treatment paradigm on parvalbumin mRNA expression was investigated. A decrease in parvalbumin mRNA was observed after chronic PCP treatment within the prelimbic region of the prefrontal cortex (controls 0.0717±0.0011, PCP 0.0536±0.0023 relative optical density (ROD)). This PCP-induced decrease was reversed by clozapine (0.0693±0.0050 ROD) but not by haloperidol (0.0557±0.0022 ROD). PCP produced a significant decrease in parvalbumin mRNA within the ventral reticular nucleus of the thalamus (controls 0.6416±0.0122, PCP 0.5032±0.0194 ROD) which was reversed by both clozapine (0.6354±0.0173 ROD) and haloperidol (0.06199±0.0137) (see Figure 12). This decrease in parvalbumin expression is in agreement with studies of

schizophrenic post mortem tissue within the prefrontal cortex (Beasley & Reynolds, 1997) and anterior thalamus (Danos et al, 1998). The ability of clozapine but not haloperidol to reverse the decrease in parvalbumin expression in the prefrontal cortex is consistent with its ability to alleviate the cognitive deficits/negative symptoms in schizophrenia. Thus, reversal of parvalbumin deficits may be a useful marker for detecting atypical antipsychotic activity.

Methods

5-HT_{2A} receptor binding: Sections from the level of the prefrontal cortex were preincubated for two consecutive washes at room temperature in 50mM Tris HCl buffer pH 7.4 to remove endogenous ligand. Total binding was defined using 0.71 nM (Wolkin, A. et al) ³H-ketanserin in the presence of 1μM prazosin and 1μM tetrabenazine (to block non 5-HT_{2A} binding). Non-specific binding was defined using 50nM spiperone. Sections were incubated with the appropriate ligand solution for 1 hour at room temperature then washed twice for 10 minutes in ice cold buffer before being rinsed in ice cold water and rapidly air dried. The sections were then exposed to film (Biomax MR, Kodak) with previously calibrated (Wolkin, A. et al) ³H-standards. Autoradiograms were analysed using MCID densitometry system. Results were statistically analysed using a one-

way ANOVA followed by a student Newman-Keuls post hoc test.

In situ hybridisation: a 45mer oligonucleotide probe was designed against bases 223-267 of the rat parvalbumin gene (GenBank accession number, A819345). In situ hybridisation was carried out according to the method of Wisden and Morris (1994).

Table 2: Effect of haloperidol and clozapine on PCP-induced hypofunction

		LCGU (μmol/100g/min)				
		vehicle				PCP
	vehicle	Clz	hal	vehicle	Clz	hal
<i>Prefrontal Cortex</i>						
mO layer I	127±7	93±4*	93±4*	104±5*	104±5*	105±4
mO layers						
II & III	138±6	109±4*	106±4*	121±6	112±6*	116±4*
mO layers						
V & VI	135±9	106±5*	102±4*	113±6	115±5*	119±4
PrL layer I	139±5	119±4*	114±4*	109±4*	118±6*	115±3*
PrL layers II						
& III	152±7	139±5	131±4	127±5*	134±7	134±4
PrL layers						
V & VI	116±5	98±4*	93±4*	97±3*	104±5	97±3*
<i>Thalamus</i>						
Rt	112±6	95±4*	86±4*	79±2*	81±2*	80±1*
MD	130±6	124±6	117±5	133±6	113±3	119±6
<i>Auditory System</i>						
Au layer I	153±5	136±6	142±9	138±3	140±5	141±8
Au layers						
II, III&IV	183±8	169±6	167±9	174±4	166±6	174±10
Au layers V						
& VI	126±2	126±4	112±9	120±2	118±4	117±7
AuD layer						
I	157±8	136±4	139±9	126±5*	135±5	133±7
		LCGU (μmol/100g/min)				
		vehicle			PCP	
	vehicle	Clz	hal	vehicle	Clz	hal
AuD layers						
II, III&IV	170±10	154±5	153±9	141±6*	152±6	156±10
AuD layers						
V & VI	122±2	115±6	108±7	105±2*	107±4	106±6*
DLL	112±5	99±5	92±4	89±4*	108±5	107±2
VLL	120±4	109±5	106±5	98±6*	118±5	110±3
cochlear						
nucleus	125±2	108±7	99±9*	92±4*	119±8	115±2
<i>Hippocampus</i>						
CA1 molecular						
layer	106±3	102±5	92±5	93±2	87±2*	97±4
CA1 stratum						

radiatum	82±3	80±4	66±4*	67±2*	66±3*	74±4
CA1 pyramidal cell layer	79±3	78±4	63±4*	63±2*	62±2*	70±4
CA1 stratum oriens	73±3	72±4	59±4*	59±2*	57±2*	64±4
CA3 molecular layer	96±2	96±4	90±4	90±2	84±2	94±6
CA3 stratum radiatum	76±2	83±5	73±1	70±3	69±2	76±5
CA3 pyramidal cell layer	75±3	81±4	71±4	69±2	69±3	74±5
CA3 stratum oriens	69±3	74±4	64±4	60±3	62±1	69±5

Table 2: All data expressed as mean LCGU ($\mu\text{mol}/100\text{g}/\text{min}$) \pm SEM (n=6). Statistical analysis carried out using individual two-way ANOVA for each discrete brain region followed by Tukey's post hoc test where appropriate, with statistical significant defined as $p < 0.05$. * $p < 0.05$ compared to controls. The treatment paradigm was as follows: once daily i.p. injections of PCP (2.58mgkg^{-1}) or vehicle (saline) on days 1 to 5 (phase 1), implantation of primed osmotic minipumps on day 8 (vehicle, clozapine $20\text{mgkg}^{-1}/\text{day}$, haloperidol $1\text{mgkg}^{-1}/\text{day}$), i.p. injections of PCP or vehicle once daily on days 8, 10, 12, 15, 17, 19, 22, 24 and 26 (phase 2) with the animals killed on day 29. Abbreviations are as in Table 1 legend.

Example 3 - Use of PCP model to discover novel genes potentially important in schizophrenia and its treatment

The PCP model as described herein has been used to identify novel genes for schizophrenia using two different molecular biology approaches.

1) Atlas Arrays

Four groups of rats were treated with (a) chronic PCP, (see Example 1), (b) chronic vehicle (control), (c) chronic PCP plus chronic clozapine and (d) chronic PCP plus chronic haloperidol.

Rats were injected with PCP (2.58mg/kg) or vehicle i.p. for 5 days according to the YRING PCP model. On day 7, they were implanted with osmotic minipumps containing either clozapine or haloperidol at concentrations that would administer drugs at 20 or 1mg/kg/day respectively, or vehicle. On the same day, the rats began a course of i.p. injections every 2.5 days with either PCP (2.58mg/kg) or vehicle. This regimen gave the following treatment groups:

I.P.	Minipump	N°
Vehicle	Vehicle	6
PCP	Vehicle	6
PCP	Clozapine	6
PCP	Haloperidol	6

21 days after minipump implantation, animals were killed by cervical dislocation and the prefrontal cortex dissected and stored at -70°C. RNA was then prepared according to the protocol below and the corresponding cDNA synthesis and hybridisation procedure were conducted using the rat Atlas Array kit according to the manufacturer's instructions (Clontech). Several genes were affected by

the treatments. Of particular interest was E3C (calcium independent alpha-latrotoxin receptor CIRL) which showed an increase after the PCP treatment regime and which was reversed by the antipsychotic drugs haloperidol and clozapine. A second experiment has been performed using the same treatment regimes with an n=4 per group (each value being pooled prefrontal cortex tissue from 3 rats).

Significant increases in CIRL were confirmed after chronic PCP and in addition there were significant increases in expression of UNC5H1 (a netrin receptor) and synapsins (1A and 1B) after chronic PCP as compared to the vehicle treated control group (see Table below)

Gene	Vehicle control	Chronic PCP	Significance; t test
CIRL-1	4542±804	9145±669	P<0.009
UNC5H1	1410±480	3936±472	P<0.015
Synapsins 1A&1B	17365±1144	23020±1412	P<0.025

Results are expressed as mean relative optical densities ± SEM. Statistical significance was defined as P<0.05. N=3/4 per group.

Protocol for RNA Preparation for Atlas Arrays

Frozen tissue already resides in the ribolyser tubes from the dissection procedure

- 1) Add 1.1ml Qiagen lysis buffer (containing β-

mercaptoethanol, final volume = 3%).

2) Perform 3 x 20sec homogenisations at 6.5g in a ribolyser.

3) Spin 3min in microfuge.

4) Decant to fresh tube and re-spin 3min.

5) Decide at this stage if you want to dilute supernatant with more lysis buffer.

6) Add equal volume of phenol/ CHCl_3 pH4.7, vortex 30sec and leave on ice for 10min.

7) Re-vortex and spin 4°C 5-10min at 1500g.

8) Decant supernatant and add 100ul H_2O . Add an equal volume of phenol/ CHCl_3 pH4.7, vortex, spin 5-10min at 1500g.

9) Decant supernatant and add 100ul H_2O . Add an equal volume of CHCl_3 , vortex, spin 5-10min at 1500g.

10) Decant supernatant to fresh tube.

11) Re-extract with more lysis buffer and proceed through steps 6-9 and pool fraction with stage 10 (do not add H_2O to supernatants).

12) Measure supernatant volume, add 0.1 vol. 2M NaOAC and 2.5 vol. (total vol.) ethanol, mix and leave at -80°C at least 1hr.

13) Spin 1500g for 15-20min at 4°C.

14) Wash pellet with 70% EtOH.

15) Spin 5min.

16) Decant supernatant, quick spin, remove rest of supernatant with a pipette.

- 17) Air dry pellet (don't over dry).
- 18) Re-suspend pellet in 60µl H₂O.
- 19) Measure OD₂₆₀.
- 20) DNase 1 treat RNA according to the MessageClean (Genhunter) protocol (except perform additional re-extraction with H₂O).
- 21) Re-suspend in as little H₂O as possible (12µl) to keep the RNA concentrated for the Atlas cDNA synthesis step.
- 22) 20ug of RNA in a final volume of 5µl is used to generate cDNA according to protocols outlined in the Atlas Array manual.

2) Further verification of the importance of CIRL

Samples of human schizophrenic brain and age matched control tissue (obtained from Professor G Reynolds, University of Sheffield) were examined by RT-PCR for changes in the expression of CIRL.

In addition, four groups of rats were treated with a) chronic PCP, chronic vehicle (control), c) chronic PCP plus clozapine and d) chronic PCP plus chronic haloperidol as detailed previously in Atlas Array experiment (p.32). RT-PCR for specific isoforms of CIRL was then conducted in the prefrontal cortex.

Method for brain tissue preparation (rat and human)

RT-PCR Protocol

Isolation of total RNA

1ml of lysis buffer (Qiagen), including 1% β -mercaptoethanol, was added to approximately 50-100mg of brain tissue. Tissue samples were homogenised using a ribolyser (Hybaid) with 3 bursts at 6.5g lasting 20 seconds each. Samples were then spun at room temperature in a microfuge for 3 minutes. The supernatant was removed and re-spun for a further 3 minutes. The supernatant was decanted to a fresh tube to which an equal volume of 70% ethanol was added. The remaining RNA isolation procedure was carried out according to the manufacturer's protocol (Qiagen).

Synthesis of cDNA

Synthesis of cDNA was carried out according to manufacturers protocols (Life Technologies). Briefly 3-5 μ g of total RNA was reverse transcribed using oligo dT priming. After cDNA synthesis, samples were aliquoted and stored at -70°C. The amount of cDNA in each aliquot would allow a PCR titration at four different cycles with an input RNA template concentration of about 75ng for each PCR reaction.

PCR

Alterations in expression levels were determined by semi-quantitative PCR. Expression levels between different samples were standardised against the amount of β -actin mRNA present in each sample. Briefly, known amounts of template were PCR amplified. Samples were removed over 4 consecutive cycles, however, the first cycle to be removed sometimes varied depending on when logarithmic amplification was detected. Samples were separated on agarose gels and stained with GelStar solution (Flowgen). Results were plotted as the \log_{10} of relative optical density of bands against increasing cycle number. Linear regression analysis was performed. For β -actin titrations, values were obtained from the intersection of the regression lines with the Y-axis. These values were standardised against a single sample. Standardisation coefficients generated at this step were used to standardise the data from target gene expression levels.

Results

The levels of CIRL1 mRNA increased in Brodman Area 11 in postmortem schizophrenic brain tissues as compared to controls suggesting that alterations in CIRL may be important in the schizophrenic disease state (see Figure 13).

Analysis of selected specific isoforms of CIRL in rat brain revealed that chronic PCP treatment reduced the

expression of CIRL1, CIRL2 (AB) and CIRL3 (AA) in the prefrontal cortex (see Figures 14, 15 and 16). There was a reversal of the PCP-induced reductions in the level of CIRL1 mRNA by the atypical antipsychotic drug clozapine but not by the typical antipsychotic drug haloperidol. Both drugs reversed the PCP-induced reductions in CIRL2 and CIRL3.

These data support CIRL as a therapeutic target for antipsychotic drug activity.

3) Differential Display

Four groups of rats were treated with (a) chronic PCP, (b) chronic vehicle (control), (c) chronic PCP plus chronic clozapine (d) chronic vehicle plus chronic clozapine (as above).

Differential display was performed according to the method of Liang and Pardee (Molecular Biotechnology, 110, 261-267, 1998). Prefrontal cortex tissue was dissected, and total RNA extracted using Qiagen's "RNeasy" kit. An oligo(dT) primer was then used for cDNA synthesis using MMLV reverse transcriptase. The cDNA template obtained was used as a basis for the polymerase chain reaction (PCR) using the Clontech "Delta" differential display kit. Various pairwise combinations of arbitrary primers and "Advantage 2" polymerase were employed according to the Clontech "Delta" differential display kit manual. Differential display products were electrophoresed on 6%

acrylamide gels and exposed to x-ray film. Bands corresponding to cDNA fragments differentially expressed between prefrontal cortex tissue from vehicle-treated animals and PCP-treated animals were excised, and reamplified using the original primers. Differential expression was then confirmed using further prefrontal cortex tissue from these treatment groups. The cDNAs with verified differential expression were sub-cloned and sequenced, and the sequence information obtained subsequently compared with the "DNA Data Bank of Japan" database, for homology with known genes or ESTs.

Three novel sequences were identified (SEQ ID No.s 1, 2, 3 and 4) as being differentially expressed as well as the previously known gene for phosphodiesterase 1 α . Further confirmation of changes in expression of the above identified nucleotide sequences was confirmed following chronic PCP treatment of the rat model by semi-quantitative RT-PCR (data not shown).

4) RT-PCR

Four groups of rats were treated with (a) chronic PCP, (b) chronic vehicle (control), (c) chronic PCP plus chronic clozapine (as above) or (d) chronic PCP plus chronic haloperidol (as above). The tissue was processed for RNA extraction and RT-PCR as described above, using primers specific for TNF α mRNA.

Acute PCP treatment reduced the levels of TNF α in rat

prefrontal cortex (see Figure 17). This effect was apparent 2hrs and 24hrs following drug treatment.

In groups of rats chronically treated with PCP and antipsychotic drugs (see p.32 for details), PCP in combination with haloperidol was significantly different from the chronic PCP group (see Figure 18).

Further studies revealed a significant increase in TNF α mRNA levels in the Orbital frontal cortex of schizophrenic patients (see Figure 19).

These results implicate TNF α in the development and treatment of schizophrenia.

Example 4 - Differentially expressed genes in human blood samples using cDNA macroarrays

Materials and methods

Human male blood samples from schizophrenics and healthy volunteers were obtained from Gartnavel Royal Hospital, Glasgow, UK, with consent. The profile of samples are shown in Table 3.

Total RNAs were isolated from human bloods using TRIzol LS Reagent (Gibco/BRL) and treated with DNase I. Four to 8 μ g of total RNAs were used as templates for cDNAs. 33 P radiolabelled cDNAs were hybridised with the AtlasTM Human Cytokine/Receptor Arrays (Clontech). The arrays were washed and then exposed to X-ray films. The

spots on the films were analysed by densitometry. Data were analysed using independent samples t-test. Statistical significance was defined as $p < 0.05$.

Results and discussion

In this study, only 24 to 93 out of 268 genes could be measured. This could be due to several reasons. Firstly, many cytokines are poorly expressed. Secondly, the efficiency of 1st strand cDNA synthesis could have been low due to usage of total RNA instead of mRNA. Because of the limited amount of samples available, total RNA was utilised. Finally, some membranes had extremely high background which could not be washed out even boiling the membranes.

At first, the expression levels of genes were compared to each of 3 housekeeping genes, ubiquitin, ribosomal protein S9 and phospholipase A2 for the purpose to correcting the amount of input RNA. Slightly different results were obtained when different housekeeping genes were used to standardise signals. So each relative expression level from 3 housekeeping genes was averaged for lowering the deviation. Only epithelial discoidin domain receptor 1, trkE (23 j) showed significant difference between schizophrenics and controls (see Figure 12). This kinase is purported to be a receptor for nerve growth factor and expressed at low levels in most tissues and expression is highest in the brain and lung (Perez et al).

A recent paper showed that trkC mRNA levels in schizophrenics were decreased in the frontal cortex (Schramm et al). TrkC is a high-affinity receptor for neurotrophin-3. Neurotrophins and their receptors have been implicated in the molecular-pathology in schizophrenia (Bayer & Falkai). TrkE might also show the same reduction with trkC.

Table 3. Profile of human blood samples

<u>Schizophrenics</u>					
Code No	Smoker	Age	Weight(kg)	Medication	Medical History
01	No	30	89	Clz 500 mg/day	14 yr
02	No	40	98	Clz 250 mg/day	20 yr
25	Yes	55	70	Clz 250 mg/day	20 yr
27	No	42	103	Clz 600 mg/day	24 yr
				Fpz 75 mg/2weeks	
34	No	46	80	Clz 100 mg/day	23 yr
				Diclofenac Sodium	
42.6±9.1					

<u>Controls</u>					
Code No	Smoker	Age	Weight(kg)	Medication	Medical History
04	Yes	32	76	-	-
24	No	44	95	-	-
28	No	27	73	-	-
32	No	35	84	-	Sore Throat
35	No	37	70	CoProxamol	-
35.0±6.3					

References

1. Goldberg, T. et al. The impact of clozapine on cognitive impairment and psychiatric symptomatology in patients with schizophrenia. *Br. J. Psychiatry* 162, 43-48 (1993).
2. Allen, R.M. & Young, S.J. Phencyclidine-induced psychosis. *Am. J. Psychiatry* 135, 1081-1084 (1978).
3. Wolkin, A. et al. Persistence of cerebral metabolic abnormalities in chronic schizophrenia as determined by positron emission tomography. *Am. J. Psychiatry* 142, 564-571 (1985).
4. Misra, A.L., Pontani, R.B. & Bartolomeo, J.G. Disposition of [^3H] phencyclidine in the rat after single and multiple doses. *Life Sci.* 27, 2501-2508 (1980).
5. Jentsch, J.D., Tran, A, Le, D, Toungren, K.D. & Roth, R.H. Subchronic phencyclidine administration reduces mesolimbic prefrontal dopamine utilisation and impairs prefrontal cortical-dependent cognition in the rat. *Neuropsychopharm.* 17, 92-99 (1997).
6. Sokoloff, L.. The 14-C-deoxyglucose method for the measurement of local cerebral glucose utilisation : theory, procedure and normal values in the conscious and anaesthetised albino rat. *J. Neurochem.* 28, 897-916 (1977).
7. Crane, A.M. & Porrino, L.J. Adaptation of the quantitative 2-[14-C]-deoxyglucose method for use in freely moving rats. *Brain Res.* 499, 87-92 (1989).
8. Laurelle, M. et al. Selective abnormalities of prefrontal serotonergic receptors in schizophrenia, a postmortem study. *Arch. Gen. Psychiatry* 50, 810-818 (1993).
9. Heritch, A.J. Evidence for reduced and dysregulated turnover of dopamine in schizophrenia. *Schiz. Bull.* 16 (4), 605-615 (1990).
10. Tamminga, C. Schizophrenia and glutamatergic transmission. *Critical. Rev. Neurol.* 12 (1&2), 21-36 (1998).
11. Angrist, B. & van Kammen D.P. CNS stimulants as a tool in the study of schizophrenia. *Trends Neurosci.* 7, 388-390 (1984).
12. Swerdlow, N.R. & Koob, G.F. Dopamine, schizophrenia, mania and depression: Toward a unified hypothesis of cortico-striato-pallido-thalamic function. *Behav. Brain Sci.* 10, 197-245 (1987).
13. Weinberger, D.R. A connectionist approach to the prefrontal cortex. *J. of Neuropsychiatry and Clinical Neurosciences* 5, 241-253 (1993).
14. Bertolino, A et al. Altered development of prefrontal neurons in rhesus monkeys with neonatal mesial temporo-limbic lesions: A proton magnetic resonance

- spectroscopic imaging study. *Cereb. Cortex* 7, 740-748 (1997).
15. Jones, G.H., Marsden, C.A. & Robbins, T.W. Increased sensitivity to amphetamine and reward-related stimuli following social isolation in rats: Possible disruption of dopamine-dependent mechanisms of the nucleus accumbens. *Psychopharmacology* 102, 364-372 (1990).
 16. Sams-Dodd, F. Phencyclidine-induced stereotyped behaviour and social isolation in rats: A possible animal model of schizophrenia. *Behav. Pharmacol.* 7, 3-23 (1996).
 17. Snyder, S.H. Psychotogenic drugs as models of schizophrenia. *Neuropsychopharm.* 1, 197-199 (1988).
 18. Wolkin, A. et al. Negative symptoms and hypofrontality in chronic schizophrenia. *Arch. Gen. Psychiatry* 49, 959-965 (1992).
 19. Tamminga, C.A. et al. Limbic system abnormalities identified in schizophrenia using positron emission tomography with fluorodeoxyglucose and neocortical alterations with deficit syndrome. *Arch. Gen. Psychiatry* 49 522-530 (1992).
 20. Perez, J.L., Shen X., Finkernagel S., Sciorra L., Jenkins, N.A., Gilbert D.J., Copeland, N.G. and Wong, T.W. (1994). Identification and chromosomal mapping of a receptor tyrosine kinase with a putative phospholipid binding sequence in its ectodomain. *Oncogene*, 9, 211-219.
 21. Schramm, M., Falkai, P., Feldmann, N., Knable, M.B. and Bayer, T.A. (1998). Reduced tyrosine kinase receptor C mRNA levels in the frontal cortex of patients with schizophrenia. *Neuroscience Letters*, 257, 65-68.
 22. Bayer, T.A. and Falkai, P. (1997). Schizophrenia a subtle defect in neurotrophic gene function? *Neurol. Psychiatr. Brain Res.*, 5, 151-156.
 23. Beasley, C.A. and Reynolds, G.P. (1997). Parvalbumin-immunoreactive neurons are reduced in the prefrontal cortex of schizophrenics. *Schiz. Res.*, 24, 349-355.
 24. Danos, P., Baumann, B., Bernstein H-G., Franz, M., Stauch, R., Northoff, G., Krell, D., Falkai, P. and Borgerts, B. (1998). Schizophrenia and anteroventral thalamic nucleus: selective decrease of parvalbumin-immunoreactive thalamocortical projection neurons.
 25. Wisen, W & Morris, B.J. In situ hybridisation with synthetic probes. In *In situ hybridisation protocols for the brain*. 9-34. Wisen, W & Morris, B.J. (Eds), Academic press, London.

CLAIMS

1. Use of one or more polynucleotide sequence(s) selected from the group consisting of SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 7, 9 and 11, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 and 19, and SEQ ID No. 21, or fragments thereof, for diagnosing schizophrenia.

2. Use of one or more polypeptide sequence(s) derived from one or more polynucleotide sequence(s) selected from the group consisting of SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 7, 9 and 11, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 and 19, and SEQ ID No. 21, or fragments thereof, for diagnosing schizophrenia.

3. A method of diagnosing schizophrenia, said method comprising using one or more polynucleotide sequence(s) selected from the group consisting of SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 7, 9 and 11, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 and 19, and SEQ ID No. 21, or fragments thereof, as indicator(s) of schizophrenia.

4. A method of diagnosing schizophrenia, said method comprising using one or more polypeptide sequence(s) derived from one or more polynucleotide sequence(s) selected from the group consisting of SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 7, 9 and 11, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 and 19, and SEQ ID No. 21, or fragments thereof, as indicator(s) of schizophrenia.

5. Use of one or more polynucleotide sequence(s) selected from the group consisting of SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 7, 9 and 11, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 and 19, and SEQ ID No. 21, or fragments thereof, in the manufacture of a medicament for the treatment of schizophrenia.

6. Use of one or more polypeptide sequence(s) derived from one or more polynucleotide sequence(s) selected from the group consisting of SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 7, 9 and 11, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 and 19, and SEQ ID No. 21, or fragments thereof, in the manufacture of a medicament for the treatment of schizophrenia.

7. An isolated polynucleotide sequence having nucleic acid sequence selected from the group consisting of SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3 and SEQ ID No. 4.

8. An isolated nucleic acid having at least 80% identity or homology with a nucleic acid sequence selected from the group consisting of SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3 and SEQ ID No. 4.

9. An isolated nucleic acid according to claim 8, wherein said nucleic acid has at least 90% identity or homology.

10. An isolated nucleic acid according to claim 8, wherein said nucleic acid is at least 15 nucleotides in length.

11. A nucleic acid which can specifically hybridize with a sequence selected from the group consisting of SEQ ID Nos. 1, 2, 3 and 4, or their complement.

12. A nucleic acid according to claim 11, wherein said nucleic acid has at least 80% sequence identity or homology with a sequence selected from the group consisting of SEQ ID Nos. 1, 2, 3 and 4, or their complement.

13. A nucleic acid according to claims 11 or 12, wherein said nucleic acid is at least 15 nucleotides in length.

14. Use of a nucleic acid as claimed in claim 13 for diagnosing schizophrenia.

15. A recombinant nucleic acid molecule comprising a polynucleotide fragment as claimed in claims 7 to 13.

16. A recombinant nucleic acid molecule according to claim 15 characterised in that the recombinant nucleic acid molecule comprises regulatory control sequences operably linked to said polynucleotide fragment for controlling expression of said polynucleotide fragment.

17. A recombinant nucleic acid molecule according to claim 16 wherein the recombinant nucleic acid molecule is a plasmid.

18. A recombinant nucleic acid molecule according to claim 16 wherein the recombinant nucleic acid molecule is derived from a viral vector.

19. A prokaryotic or eukaryotic host cell transformed by a polynucleotide fragment or recombinant molecule according to any of claims 7 to 17.

20. Use of one or more polynucleotide sequence(s) selected from the group consisting of SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 7, 9 and 11, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 and 19, and SEQ ID No. 21, or fragments thereof, in the identification of compounds which modulate the expression of said polynucleotide sequence(s).

21.. Use of one or more polypeptide sequence(s) derived from one or more polynucleotide sequence(s) selected from the group consisting of SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 7, 9 and 11, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 and 19, and SEQ ID No. 21, or fragments thereof, in the identification of compounds which modulate the expression of said polypeptide sequence(s).

22. Use of a polynucleotide or polypeptide sequence according to claims 20 or 21, wherein said identified compound results in overexpression of said polynucleotide or polypeptide sequence.

23. Use of a polynucleotide or polypeptide sequence according to claims 20 or 21, wherein said identified compound results in underexpression of said polynucleotide or polypeptide sequence.

24. An antisense nucleotide fragment complimentary to a polynucleotide fragment or subfragment selected from the group consisting of SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 7, 9 and 11, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 and 19, and SEQ ID No. 21, or fragments thereof.

25. Use of an antisense nucleotide fragment complimentary to a polynucleotide fragment or subfragment selected from the group consisting of SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 7, 9 and 11, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 and 19, and SEQ ID No. 21, or fragments thereof, in the manufacture of a medicament for the treatment of schizophrenia.

26. A method for screening a compound which regulates expression of a schizophrenia-related gene(s), said method comprising:

(a) bringing a test compound into contact with transformed cell which enables expression of a gene selected from the group consisting of SEQ ID No. 1, SEQ ID

No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5 (PDEI α),
SEQ ID No. 7, 9 & 11 (CIRL 1, 2 & 3), SEQ ID No. 13 (trkE),
SEQ ID No. 15 (netrin receptor, SEQ ID No. 17 & 19
(aynapsin 1A/AB), and SEQ ID No. 21 (TNF α),

(b) detecting an expression of schizophrenia-relating factor in said cell, and

(c) selecting a compound which promotes or suppresses an induction of the schizophrenia-relating factor in comparison with a control (vehicle).

27. A method for measuring an anti-schizophrenic effects of a compound using the animal model of the present invention, which comprises:

(a) measuring local cerebral glucose utilisation (LCGU), or detecting an expression level of one or more genes represented by the group consisting of SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5 (PDEI α), SEQ ID No. 7, 9 & 11 (CIRL 1, 2 & 3), SEQ ID No. 13 (trkE), SEQ ID No. 15 (netrin receptor, SEQ ID No. 17 & 19 (aynapsin 1A/AB), and SEQ ID No. 21 (TNF α), and

(b) comparing with a control group.

28. A transgenic animal wherein the expression of one or more genes containing nucleotide sequences selected from consisting of SEQ ID Nos. 1, 2, 3, 4, 5, 7, 9, 11, 13, 15, 17, 19 and 21 has/have been modulated in vivo.

29. A cell line wherein the expression of one or more genes containing nucleotide sequences selected from consisting of SEQ ID. Nos. 1, 2, 3, 4, 5, 7, 9, 11, 13, 15, 17, 19 and 21 has/have been modulated.

30. An antibody immuno-reactive with a polypeptide or fragment thereof derived from a polynucleotide fragment selected from the group consisting of SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3 and SEQ ID No. 4.

31. Use of an antibody immuno-reactive with a polypeptide, or fragment thereof, derived from a polynucleotide fragment selected from the group consisting of SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 7, 9 and 11, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 and 19, and SEQ ID No. 21 for diagnosing schizophrenia.

32. A pharmaceutical composition comprising a polynucleotide fragment, or derivative thereof, according to any of claims 7 to 13 together with a pharmaceutically acceptable carrier.

33. A pharmaceutical composition comprising a polypeptide fragment, or derivative thereof, according to claim 32 together with a pharmaceutically acceptable carrier.

34. Use of one or more polypeptide sequence(s) derived from one or more polynucleotide sequence(s) selected from the group consisting of SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 7, 9 and 11, SEQ ID No. 13, SEQ ID No. 15, SEQ ID No. 17 and 19, and SEQ ID No. 21, or fragments thereof, for testing candidate compounds for any effect on said polypeptide(s).

35. A chronic animal model of schizophrenia.

36. A chronic animal model according to claim 35, wherein said animal model has been developed by the addition of PCP to an animal.

37. A method for developing a chronic animal model of schizophrenia said method comprising the steps of:

(a) administering PCP to an animal in order to induce a psychotic state in the animal representative of the onset of schizophrenia in humans; and

(b) further administering of PCP in order to maintain the PCP-induced psychotic state in the animal,

over a period of time, to mimic a chronic state of schizophrenia in the animal.

38. A method according to claim 37 wherein the dose of PCP used to induce a psychotic state in said animal is in the range of 1 to 5 mgkg⁻¹.

39. A method according to claim 38 wherein the dose of PCP used to induce a psychotic state in said animal is in the range of 2 to 4 mgkg⁻¹.

40. A method according to claim 39 wherein the dose of PCP used to induce a psychotic state in said animal is about 2.58mgkg⁻¹.

41. An animal model produced by the method according to any one of claims 37 to 40.

42. An animal model according to claims 35, 36 or 41 wherein the animal is selected from the group consisting of rat, mouse, guinea pig or rabbit.

43. Use of the animal model as claimed in any of claims 35, 36, 41 or 42 for screening new drugs for the treatment of schizophrenia.

44. Use of the animal model as claimed in any of claims 35, 36, 41 or 42 in the identification of genes associated with the schizophrenic state.

45. A method for screening an atypical antipsychotic drug which comprises using parvalbumin or CIRL1 as an indicator.

1/23

FIGURE 1

Gene sequence for YSG 3 (SEQ ID NO.1) rat

TCCAGACTCTGAAAGCACACAAGAACGGTTCATGGAATCTNAGCAAAGCCTAACCAAGAAA
AGCTCCAGTTCCTCCTGTTTCGGCAGGGCGTGGGCATCGGCAGTGCCAGGGAATGCTTGGT
GCATGAACAGGACCCCCAGGTGAGCCATATTTGCAGTAAGAGTCATCAGCATTGCTCCTG
AGAAGCCTCAGGCTCAGAAGAAAGCTTTTGCTAGCAAATTGTTAGGGTCTGGGAAGTAAT
GCTCAGGGCTAGGATAGCATACCCAAGGCCCGTGCTGCATCCCAACACTG

FIGURE 2

Gene sequence for YSG 4 (SEQ ID No. 2)

AACATTCCAAACAAAAGACACTAATATTTAGGCATGCATGTGATCTTGTTCAACTTCTCT
GTTTTTAGTTATTTGTGTAAACATTATCATTACGAATTGCATTTTTTGAACTTTTCTATT
TTCAGGCAATGAGAACAAATACAGAGGTACAGAACTAAGTATTACACACGCACACACACA
CACACACACACACACACACAGAGAGAGAGAGAGAGAGAGAGAGAGAGAGAGAGAGAGA
GAGAGAGAGAGAAGGGAAGGTAAAGGTGGACTTAAAAAACATTGCTCTAAATGGGAAGTC
TCAAGCAAGTCTCTTCACTCAGACCTCGGGGGTCCTTCAT

FIGURE 3

Gene sequence for YSG 6 (SEQ ID No.3) rat

GCAGGATGCAACCGGACATTTCTCCTTTGTAGAGTGAGGATCCACAGAAGTGTTGTGAT
ACCCGAAGGGCAGCAGCAGGCTGCTGCTGTGTCTGTGATATTAAATCCCATTGTTAATCA
CTAAGGATTAATTGTTAAAGGATAAACACAAGGTGTTTGTGTTGGCTCCCAGCAATCTTGA
AATTAAATAAGAAAGGAGGTTTGGGACCAACTCCTGAGTGAGTAGATAGCCCTAGAAGGA
ACTGCTTCACCCAGAACCTGGGTCCCAGGGTTCTAGACCAGGGAGGGGCCAAGCAAGTGA
ATGGTTTTTGCCAGGAAGCTGGAACCTAAGGAGCTGTTTGGCAGG

Figure 4

Gene sequence for YSG 9 (SEQ ID No. 4) rat

CACAGCCTCTGTTAAAAGGCATCTGGGTCTTGGTAAATGGCTTTTTATCTGTGTTATTTA
TGTGTCCAACATTTTATGTGTGTGCCGAGTTCAGAGGGTAAGCCCACATGCTACCACAGA
CTCAGCCAGGGAAATCCAGTACAATGGGTCCAAGCACTTAATTCATTAATTTATTTTTGA
GACAGCCACGTGTAGCCCAGGGTGGCTTTAAACTCACAATGTAGCAGAGGCTGGCTTTGA
ACTTTTTATCCTCCTGATTCTAATTCCTATGCTAGAATTAGAGGCTTTTGCCACCA

FIGURE 5aGene sequence for YSG1 (SEQ ID No.5)
(phosphodiesterase 1 α , rat)

ATGGCAAGACAAGGCTGTCTCGGGTCATTCCAGGTAATATCCTTGTTTCAC
TTTTGCCATCAGTGTCAATATCTGCTTAGGATTCACAGCAAGTCGAATTA
AGAGGGCAGAATGGGATGAAGGACCTCCACAGTGCTGTCTGACTCTCCA

2/23

TGGACCAACACCTCTGGATCCTGCAAAGGTAGATGCTTTGAGCTTCAAGA
GGTTGGCCCTCCAGACTGTCGGTGTGACAACCTGTGTAAGAGCTACAGCA
GCTGCTGCCACGATTTTCGATGAGCTCTGTTTGAAAACAGTCCGAGGCTGG
GAGTGCACCAAGACAGAAGTGGGGAAGTACGAAACGAGGAAAATGCCTG
TCACTGCCCAGAAGACTGCTTGTCCAGGGGAGACTGCTGTACCAACTACC
AAGTGGTCTGCAAAGGAGAATCACACTGGGTAGATGATGCTGCGAGAAAT
CAAAGTTCCGAATGCCTGCAGGTTTGTCCGCCTCCGTTAATCATCTTCTC
TGTGGATGGTTTCCGTGCATCATACATGAAGAAAGGCAGCAAGGTTATGC
CCAACATTGAGAACTGCGGTCTGTGGCACCCTATGTCCTTACACGAGG
CCTGTGTACCCCAAAAACCTTCCCTAATCTATATACGCTGGCCACTGG
TTTATATCCGGAATCCCATGGAATTGTTCGGTAATTCAATGTATGATCCTG
TCTTTGATGCTTCGTTCCATCTACGAGGGCGAGAGAAGTTTAATCATAGG
TGGTGGGGAGGCCAACCGCTATGGATTACAGCCACCAAGCAAGGGGTGAG
AGCTGGAACATTCTTTTGGTCTGTGAGCATCCCTCATGAACGGAGGATCC
TAACCATTTCTCAGTGGCTTTCTCTGCCAGACAACGAGAGGCCTTCAGTT
TATGCCTTCTACTCAGAGCAGCCTGATTTTTCTGGACACAAGTACGGCCC
TTTTGGCCCTGAGATGACAAATCCTCTGAGGGAGATTGACAAGACCGTGG
GGCAGTTAATGGATGGACTGAAACAACTCAGGCTGCATCGCTGTGTGAAC
GTTATCTTTGTTGGAGACCATGGAATGGAAGATGTGACATGTGACAGAAC
TGAGTTCTTGAGCAACTATCTGACTAATGTGGATGACATTACTTTAGTGC
CTGGAACCTCTGGGAAGAATTCGAGCCAAATCTATCAATAATTCTAAATAT
GACCCTAAAACCATTTATTGCTAACCTCACGTGCAAAAAACCGGATCAGCA
CTTTAAGCCTTACATGAAACAGCACCTTCCCAAACGGTTGCACTATGCCA
ACAACAGAAGAATTGAAGACATCCATTTATTGGTCGATCGAAGATGGCAT
GTTGCAAGGAAACCTTTGGACGTTTATAAGAAACCATCAGGAAAATGTTT
TTTCCAGGGTGACCACGGCTTTGATAACAAGGTCAATAGCATGCAGACTG
TTTTCGTAGGTTATGGCCCACTTTTAAAGTACAGGACTAAAGTGCCTCCA
TTTGAAAACATTGAACTTTACAATGTTATGTGCGATCTCCTAGGCTTGAA
GCCCCGCTCCCAATAATGGAATCATGGAAGCTTGAATCACCTACTGCGTA
CAAATACCTTTTAGGCCAACCATGCCAGACGAAGTCAGCCGACCTAACTAC
CCAGGGATTATGTACCTTCAGTCCGAGTTTGACCTGGGCTGCACCTGTGA
CGATAAGGTAGAGCCAAAGAACAAATTTGGAAGAACTCAATAAACGTCTTC
ATACCAAAGGATCAACAGAAGCTGAAACCGGGAAATTCAGAGGCAGCAAA
CATGAAAACAAGAAAAACCTTAATGGAAGTGTGTAACCTAGAAAAGAGAG
ACATCTCCTGTATGGACGGCCTGCAGTGCTCTATCGGACTAGCTATGATA
TCTTATACCATACGGACTTTGAAAGTGGTTATAGTGAAATATTTCTTAATG
CCTCTCTGGACATCGTATACCATTTCTAAGCAGGCTGAGGTCTCCAGCAT
CCCAGAACACCTGACCAACTGTGTTTCGTCCTGATGTCCGTGTGTCTCCAG
GATTCAGTCAGAACTGTTTAGCTTATAAAAAATGATAAACAGATGTCATAT
GGATTCCTTTTTTTCCTCCCTACCTGAGCTCCTCCCCAGAAGCTAAGTATGA
TGCATTTCCTCGTAACCAACATGGTTCCAATGTACCCCGCCTTCAAACGTG
TTTGGGCTTATTTCCAAAGGGTTTTTGGTGAAGAAATATGCTTCAGAAAGG
AATGGAGTCAACGTAATAAGTGGACCGATTTTTTGACTACAATTACGATGG
CCTACGTGACACTGAAGATGAAATTAAACAGTATGTGGAAGGCAGCTCTA
TACCTGTCCCCACCCACTACTACAGCATCATCACCAGCTGCCTGGACTTC
ACTCAGCCTGCAGACAAGTGTGACGGTCCCCTCTCTGTGTCTTCCTTCAT
CCTTCCTCACCGACCCGACAATGATGAGAGCTGTAATAGCTCCGAGGATG
AGTCGAAGTGGGTAGAGGAACTCATGAAGATGCACACAGCTCGGGTGCGG
GACATTGAGCACCTCACTGGTCTGGATTTCTACCGGAAGACTAGCCGTAG

3/23

CTATTTCGGAAATTCTGACCCTCAAGACATACCTGCATACATATGAGAGCG
AGATTTAA

FIGURE 5b

Peptide sequence for YSG1 (SEQ ID No.6)
(phosphodiesterase 1 α , rat)

MARQGCLGSFQVISLFTFAISVNICLGFTASRIKRAEWDEGPPTVLSDSP
WTNTSGSCKGRCFELQEVGPPDCRCDNLCKSYSSCCHDFDELCLKTVRGW
ECTKDRSGEVRNEENACHCPEDCLSRGDCCTNYQVVCKGESHWVDDAARN
QSSECLQVCPPLIIFSVDGFRASYMKKGSKVMPNIEKLRSCGTHVPYTR
PVYPTKTFPNLYTLATGLYPESHGIVGNSMYDPVFDASFHLRGREKFNHR
WWGGQPLWITATKQGVRACTFFWSVSI PHERRILTLQWLSLPDNERPSV
YAFYSEQPDFSGHKYGFPGPEMTNPLREIDKTVGQLMDGLKQLRLHRCVN
VIFVGDHGMEDVTCDRTEFLSNYLTVNDDITLVPGLGRIRAKSINNSKY
DPKTI IANLTCKKPDQHFQKPYMKQHLPKRLHYANNRRIEDIHLLVDRRW
VARKPLDVYKKPSGKCFQGDHGFNDKVNNSMQTVFVGYPGTFKYRTKVPP
FENIELYNVMCDLLGLKPAPNNGTHGSLNHLRLTNTFRPTMPDEVSRPNY
PGIMYLQSEFDLGCTCDDKVEPKNKLEELNKRHLTKGSTEAETGKFRGSK
HENKKNLNGSVEPRKERHLLYGRPAVLYRTSYDILYHTDFESGYSEIFLM
PLWTSYTISKQAEVSSIPEHLTNCVRPDVRVSPGFSQNCCLAYKNDKQMSY
GFLFPPYLSSSPEAKYDAFLVTNMVPMYPAFKRVWAYFQRLVVKYASER
NGVNVISGPIFDYNYDGLRDEDEIKQYVEGSSIPVPTHYYSIITSCLDF
TQPADKCDGPLSVSSFILPHRPDNDSCNSSEDESKWVEELMKMHTARVR
DIEHLTGLDFYRKTSRSYSEILTLKTYLHTYESEI

FIGURE 6a

Gene sequences for YSG2 (SEQ ID No.7) (CIRL, rat)
CIRL-1 variant BB (other variants: AA, AB, BA)

ATGGCCCGCTTGGCTGCAGCACTCTGGAGTCTCTGTGTGACGACTGTCCT
CGTCACCTCTGCTACCCAAGGCCTGAGCCGGGCTGGACTCCCATTGCGAT
TGATGCGCCGGGAGCTAGCATGCGAAGGCTACCCCATGAGCTGCGGTGC
CCGGGCAGTGACGTCATCATGGTGGAGAATGCAAACCTATGGGCGCACAGA
TGACAAGATCTGCGATGCCGACCCCTTTTCAGATGGAGAACGTGCAGTGCT
ACCTGCCTGACGCCTTCAAATCATGTACAGAGATGTAATAACCGAACC
CAGTGTGTGGTGGTGGCCGGCTCTGACGCCTTTCCTGACCCCTGTCCTGG
AACCTACAAGTACCTGGAGGTGCAGTACGACTGTGTCCCTTACAAAGTGG
AGCAGAAAGTCTTCGTGTGCCAGGGACACTGCAGAAGGTGCTGGAGCCC
ACCTCCACACATGAATCGGAGCACCAGTCTGGCGCATGGTGCAAGGACCC
ACTGCAGGCAGGTGACCGTATCTACGTTATGCCCTGGATCCCCTACCGCA
CGGACACACTGACCGAGTATGCTTCCTGGGAGGACTATGTGGCTGCACGC
CACACCACACGTACAGACTGCCCAACCGTGTAGATGGCACTGGCTTTGT
GGTATATGATGGTGCCGTCTTCTATAACAAGGAACGTACTCGCAACATTG
TCAAATATGACCTGCGGACCCGCATCAAGAGCGGAGAAACAGTCATAAAC
ACAGCCAACTACCACGACACCTCACCTTATCGCTGGGGAGGCAAAACCGA
CATTGACCTGGCAGTGGATGAGAACGGGCTGTGGGTCATCTATGCCACCG

AGGGGAACAACGGGGCGTCTGGTGGTGAGCCAGCTCAACCCCTACACACTG
CGTTTCGAGGGCACCTGGGAAACAGGCTATGACAAGCGCTCAGCCTCCAA
TGCCTTCATGGTGTGTGGTGTCTCTATGTGCTGCGCTCTGTTTATGTGG
ATGACGACAGTGAGGCAGCAGGCAACCGCGTGGACTATGCCTTTAACACC
AATGCAAACCGAGAGGAGCCCGTCAGTCTCGCCTTCCCCAACCCCTACCA
GTTTGTATCTTCTGTTGACTACAATCCCCGGGACAACCAGCTGTATGTGT
GGAACAACCTATTTCTGTTGGTGCGCTACAGCCTGGAGTTTGGACCCCCAGAT
CCCAGTGCTGGCCCAGCCACTTCCCCACCTCTCAGTACCACCACCACAGC
TCGGCCTACGCCCCCTCACCAGCACAGCCTCACCTGCAGCCACCCTCCAC
TCCGCCGGGGCGCCCCCTCACCACGCACCCAGTAGGTGCCATCAACCAGCTG
GGACCTGACCTGCCTCCAGCCACAGCCCCAGCACCCAGTACCCGGCGGGCC
TCCAGCCCCCAATCTGCATGTGTCCCCTGAGCTCTTCTGTGAACCCCCGAG
AGGTCCGGCGGGTCCAGTGGCCAGCTACCCAGCAGGGTATGCTGGTAGAG
AGACCTTGCCCCAAGGGAACCTCGAGGAATTGCCTCGTTCCAGTGCCTCCC
AGCTCTGGGGCTCTGGAATCCTCGGGGCCCTGACCTCAGCAACTGCACCT
CCCCCTGGGTCAACCAAGTCGCCCCAGAAGATCAAGAGTGGAGAGAATGCA
GCCAACATTGCTAGTGAGCTGGCCCGCCACACGCGGGGCTCCATCTATGC
TGGGGACGTGTCTCTCATCGGTGAAGCTGATGGAGCAACTGCTAGATATCC
TGGATGCCCAGCTCCAGGCCCTACGGCCCATTGAACGAGAGTCAGCTGGC
AAGAACTACAATAAGATGCACAAGCGAGAGAGAACCTGCAAGGACTATAT
CAAGGCTGTGGTGGAGACAGTGGACAACCTGCTTCGGCCAGAGGCACTTG
AGTCATGGAAAGACATGAATGCCACCGAACAGGTCCATACGGCCACCATG
CTCCTAGATGTCTTAGAGGAGGGTGCCTTCCTGCTGGCCGACAATGTGAG
AGAACCTGCTCGCTTCTTGGCTGCCAAGCAGAATGTGGTTCCTGGAGGTCA
CTGTCCTGAGCACAGAGGGTCAAGTGCAGGAGTTGGTGTTCCCCCAGGAG
TATGCCAGTGAGAGCTCCATTCAGCTGTCCGCCAACACCATCAAGCAGAA
CAGCCGCAATGGTGTGGTGAAGGTTGTCTTCATTCTCTACAACAACCTGG
GCCTCTTCTTGTCCACGGAGAATGCCACAGTGAAGCTGGCAGGTGAGGCA
GGGACCGGTGGCCCTGGAGGTGCCTCCCTGGTGGTTAACTCACAGGTCAT
CGCAGCATCCATCAATAAGGAGTCCAGCCGTGTCTTCCTCATGGACCCTG
TCATCTTTACTGTGGCCCACTTGGAGGGCCAAGAACCACTTCAATGCAAAC
TGCTCCTTCTGGAACCTACTCAGAGCGCTCCATGCTGGGCTACTGGTCAAC
CCAGGGCTGCCGACTGGTGGAGTCCAATAAGACCCATAACCACATGTGCCT
GCAGCCACCTCACCAACTTCGCAGTGCTCATGGCTCACCGAGAGATCTAC
CAAGGCCGTATTAATGAGCTGTTGCTGTGAGTCATCACCTGGGTTGGCAT
TGTATCTCCCTGGTCTGTCTGGCTATCTGCATCTCCACCTTCTGCTTCC
TGCGGGGCTGCAGACCGACCGCAACACCATCCACAAGAACCTGTGCATC
AACCTCTTCCTTGCAGAGCTGCTCTTCCTGGTTGGAATAGACAAAACCTCA
GTATGAGGTGCCTGCCCTATCTTTGCGGGCCTGCTGCACTACTTCTTCC
TGGCCGCCTTCTCCTGGCTGTGCCTAGAGGGCGTGACCTCTACCTCCTG
CTGGTCGAGGTGTTTCGAGAGCGAATATTCACGCACCAAGTACTATTACCT
GGGCGGCTACTGCTTCCCAGCCCTGGTGGTAGGCATCGCAGCCGCCATTG
ACTACCGAAGCTACGGCACTGAGAAGGCCTGCTGGCTGAGGGTGGATAAC
TATTTTCATCTGGAGCTTCATTGGGCCCCGTCTCCTTTGTTATTGTGGTGAA
CCTGGTGTTCCTCATGGTGACCCTGCACAAGATGATCCGAAGCTCATCCG
TGCTCAAGCCTGACTCCAGCCGCCTTGACAACATCAAGTCCTGGGCGCTG
GGTGCCATTGCACTGCTCTTCCTGCTGGGCCCTCACCTGGGCTTTTCGGCCT
CCTCTTCATCAACAAGGAGTCAGTAGTAATGGCTTACCTCTTCACAACCT
TCAACGCCTTCCAGGGGGTCTTCATCTTTGTCTTTCACTGCGCCTTACAG

5/23

AAAAAGGTGCACAAGGAGTACAGCAAGTGCCTGCGTCACTCCTACTGCTG
CATTCGCTCCCCACCTGGGGGGGCTCACGGCTCCCTTAAGACCTCAGCCA
TGCGAAGTAACACCCGCTACTACACAGGGACCCAGGTACCCGGGCAGGGA
AGGCATATCCACCAGGTCTCTCTGCGGGCCGAGAGGCAGGAGTGCTCTGCC
AGAGTCTCAGAAAGATCCTGGAGGGCAGAGTGGTCTGGAGACCCCCCTCA
CGTTTGGGCTGTGTCCCAGCCGAATCCGGAGGATGTGGAATGACACCGTG
AGGAAGCAGACAGAGTCGTCCTTTATGGCAGGGGACATCAACAGCACCCC
CACCCCTGAACCGAGGTACCATGGGGAACCACTACTGACCAACCCTGTGC
TACAGCCCCGTGGGGGCACTAGCCCATACAATACTCATTCAGAGTCT
GTGGGCTTCAATCCCTCCTCGCCCCCAGTCTTCAACTCCCCAGGAAGCTA
CAGGGAACCTAAGCACCCCTTGGGCGGCCGGAAGCCTGTGGCATGGACA
CACTGCCCCCTAATGGCAACTTCAACAACAGCTACTCCTTGCGAAGTGGT
GATTTCCCTCCGGGGGATGGGGGTCTGAGCCACCCCGAGGCCGAAACCT
AGCGGATGCTGCGGCCTTTGAGAAGATGATCATCTCAGAGCTGGTGACA
ACAACCTTCGGGGGGCCAGTGGGGGCGCCAAAGGTCTCCACCAGAGCCT
CCTGTGCCACCCGTGCCAGGAGTCAGTGAGGACGAGGCTGGTGGGCCTGG
GGTGCTGACCGGGCTGAGATTGAACTTCTCTACAAGGCCCTGGAGGAGC
CACTGCTGCTGCCCCGGGCCAGTCGGTGCTGTACCAGAGTGATCTGGAT
GAGTCGGAGAGCTGTACGGCAGAGGATGGGGCCACCAGCCGGCCCCCTCTC
CTCCCCCTCCCGGCCGGGACTCCCTCTATGCCAGCGGGGCCAACCTGCGGG
ACTCGCCCTCCTACCCGGACAGCAGCCCCGAAGGGCCTAATGAGGCCCTG
CCCCCTCCCCACCTGCTCCCCCTGGGCCCCCAGAAATCTACTACACCTC
TCGCCCCGCCGCCCTGGTGGCTCGGAATCCCCTACAGGGCTACTACCAGG
TGCGGCGGCCAGCCATGAGGGCTACCTGGCAGCCCCCAGCCTTGAGGGG
CCAGGGCCCCGATGGGGATGGGCAATGCAGTTGGTCACTAGTCTCTGA

FIGURE 6b

Peptide sequences for YSG2 (SEQ ID No.8) (CIRL, rat)
CIRL-1 variant BB

MARLAAALWSLCVTTVLVTSATQGLSRAGLPFGLMRRELACEGYPIELRC
PGSDVIMVENANYGRITDDKICDADPFQENVQCYLPDAFKIMSQRNNRT
QCVVVGSDAFPDPCPGTYKYLEVQYDCVPYKVEQKVFCVPGTLQKVLEP
TSTHESEHQSGAWCKDPLQAGDRIYVMPWIPYRTDTLLEYASWEDYVAAR
HTTTYRLPNRVDGTGFVVYDGAFFYNKERTRNIVKYDLRTRIKSGETVIN
TANYHDTSPYRWGGKTDIDLAVDENGLWVIYATEGNNGRLVVSQNLNPYTL
RFEGTWETGYDKRSASNAFMVCGVLYVLRSVYVDDDSEAAGNRVDYAFNT
NANREEPVSLAFPNPYQFVSSVDYNPRDNQLYVWNNYFVVRYSLFEGPPD
PSAGPATSPPLSTTTTARPTPLTSTASPAATTPLRRAPLTTHPVGAINQL
GPDLPATAPAPSTRPPAPNLHVSPELFCEPREVRRVQWPATQQGMLVE
RPCPKGTRGIASFQCLPALGLWNPRGPDLSNCTSPWVNQVAQKIKSGENA
ANIASELARHTRGSIYAGDVSSSVKLMEQLLDILDAQLQALRPIERESAG
KNYNKMHKRERTCKDYIKAVVETVDNLLRPEALESWKDMNATEQVHTATM
LLDVLEEGAFLLADNVREPARFLAAKQNVVLEVTVLSTEGQVQELVFPQE
YASESSIQLSANTIKQNSRNGVVKVVFILYNNLGLFLSTENATVKLAGEA
GTGGPGGASLVVNSQVIAASINKESSRVFLMDPVI FTVAHLEAKNHFAN
CSFWNYSERSMLGYWSTQGCRLVESNKTHTTACSHLTNFAVLMAHREIY
QGRINELLLSVITWVGIVISLVCLAICISTFCFLRGLQTDNRNTHKNLCI

6/23

NLFLAELLFLVGIDKTQYEVACPIFAGLLHYFFLAAFSWLCLEGVHLYLL
LVEVFESSEYSRTKYYYLGGYCFPALVVGIAAAIDYRSYGTEKACWLRVDN
YFIWSFIGPVSFVIIVNLVFLMVTLHKMIRSSSVLKPDSRLDNKSWAL
GAIALLLFLGLTWAFGLLFINKESVVMAYLFTTFNAFQGVFIFVFHICALQ
KKVHKEYSKCLRHSYCCIRSPPGGAHGS�KTSAMRSNTRYTGTQVPGQG
RHIHQVSLGPRGRSALPESQKDPGGQSGPGDPLTFGLCPSRIRRMWNDTV
RKQTESSFMAGDINSTPTLNRGTMGNHLLTNPVLQPRGGTSPYNTLIAES
VGFPNPSSPPVFNSPGYSYREPKHPLGGREACGMDTLPLNGNFNNSYSLRSG
DFPPGDGGPEPPRGRNLADAAFEKMIISELVHNNLRGASGGAKGPPPEP
PVPPVPGVSEDEAGGPGGADRAEIELLYKALEEPLLLPRAQSVLYQSDLD
ESESCTAEDGATSRLSSPPGRDSLYASGANLRDSPSYPDSSPEGPNEAL
PPPPPAPPGPPEIYYTSRPPALVARNPLQGYQVRRPSHEGYLAAPSLEG
PGPDGDGQMQLVTSL

FIGURE 6c

Gene sequences for YSG2 (SEQ ID No.9) (CIRL, rat)
CIRL-2 variant BC (other variants: AA, AB, AC, BA, BB)

ATGGTGTCTTCTGGTTGCAGAATGCGAAGTCTCTGGTTTATCATGATAAT
CAGTTTCTCACCGAATACCGAAGGTTTCAGCAGAGCAGCCTTGCCATTGCG
GGTTAGTTAGACGAGAGCTGTCTGTGAAGGTTATTCTATAGACCTGCGA
TGTCCGGGCAGTGACGTCATCATGATCGAGAGCGCAAACCTACGGTCCGGAC
GGACGACAAGATCTGCGACGCAGACCCCTTTCAGATGGAGAACACAGACT
GCTACCTCCCTGATGCCTTCAAATCATGACTCAAAGGTGCAACAACCGA
ACACAGTGTGTAGTAGTTACCGGGTCAGATGTATTTCTGATCCATGTCC
CGGAACTTACAAATACCTTGAAGTTCAATATGAATGTGTCCCTTACATGG
AGCAAAAAGTTTTTGTGTGTCTTGAACCTTGAAAGCAATTGTGGACTCT
CCAAGTATCTATGAAGCTGAGCAAAAGGCAGGTGCTTGGTGCAAGGACCC
CCTTCAGGCTGCAGATAAAATTTATTTTATGCCCTGGACTCCCTACCGCA
CCGATACCTTAATAGAATATGCTTCTTTAGAAGATTTTCAAACAGCCGC
CAGACAACAACATACAACTTCCAAACCGAGTGGACGGTACTGGATTTGT
GGTGTATGACGGGGCAGTCTTCTTCAACAAAGAAAGAACGAGAAACATTG
TTAAATTTGACTTGAGGACTAGAATCAAGAGTGGGGAGGCCATAATCAAC
TACGCCAACTACCATGACACCTCACCTACAGATGGGGGGGAAGACTGA
CATTGACCTGGCAGTGGATGAAAATGGCTTGTGGGTCTCTACGCCACCG
AGCAGAACAACGGAATGATCGTGATTAGCCAGCTCAATCCGTACACTCTC
CGATTTCGAAGCAACCTGGGAGACGACGTATGACAAGCGTGCGGCGTCCAA
TGCTTTTCATGATATGCGGGGTCTCTACGTGGTCAGGTCAAGTGTACCAAG
ACAATGAAAGCGAAGCTGGCAAGAAGCTCATCGACTACATTTACAACACA
AGGTTGAGCCGGGGAGAGCACGTGGACGTTCCCTTCCCCAACCAAGTACCA
GTACATCGCTGCAGTGGATTACAACCAAGAGACAACCAACTCTACGTAT
GGAACAATAACTTTATCTTACGGTATTCTCTGGAGTTTGGTCCACCCGAC
CCTGCCCAAGTGCCTACCACAGCTGTGACAATAACTTCTTCAGCTGAGCT
GTTCAAACCAACAGTGTCAACCACAAGCAGTACTTCACAGAGAGGCCCCG
TGAGCAGCACAGTCGCTGGTCTCAGGAAGGAAGCCGAGGGACAAAGCCA
CCTCCAGCAGTCTCTACAACCAAAATTCCTCCTGTAACAAATATTTTCC
CCTGCCAGAGAGATTCTGCGAAGCGTTAGAAATGAAGGGGATAAAGTGGC
CTCAGACACAAAGGGGGATGATGGTTGAGCGACCGTGTCCCAAGGGAACA

7/23

AGAGGAACGGCCTCGTATCTCTGCATGGCTTCCACAGGAACCTGGAACCC
GAAGGGCCCGGATCTTAGCAACTGCACCTCTCACTGGGTGAATCAGCTGG
CCCAGAAGATCAGAAGTGGAGAGAATGCTGCAAGTCTGGCCAACGAACTG
GCTAAGCACACCAAGGGGACGGTGTTCGCTGGGGATGTGAGCTCCTCTGT
GAGACTGATGGAACAGTTGGTGGACATCCTGGATGCCAGCTGCAGGAGC
TGAAACCGAGCGAGAAGGACTCGGCCGGGAGGAGTTATAACAAGCTCCAA
AAACGAGAGAAGACATGCAGGGCTTACCTTAAGGCCATTGTGGACACAGT
AGATAACCTTCTGAGAGCCGAGACTTTGGACTGCTGGAAACACATGAATT
CCTCAGAGCAGGCGCACACAGCCACCATGCTGTTGGACACCTTGGAAGAA
GGAGCATTTGTCTTGGCAGACAACCTTTTGGAAACCAACCCGGGTCTCAAT
GCCAACGGATAATATTGTTCTAGAAGTCGCTGTCCTCAGCACGGAAGGAC
AGGTCCAAGACTTCACCTTCCATCTCGGCTTCAAGGGGGCCTTCAGCTCC
ATCCAGCTCTCAGCCAACACCGTCAAGCAAAACAGCAGAAACGGGCTGGC
AAAGGTGGTATTTCATCATTACCGGAGTCTGGGACCATTCTTGAGCACCG
AAAATGCGACCGTCAAACCTGGGCGCAGACCTCCTGGGTGCGAACAGCACC
ATCGCAGTGAACCTCGCACGTCCTTTCAGTCTCCATCAATAAGGAGTCCAG
CCGTGTGTACTTGACAGACCCGGTGCTTTTTTCAATGCCACACATTGATT
CTGACAATTATTTCAACGCAAACCTGCTCCTTCTGGAACCTACTCAGAGAGA
ACCATGATGGGATATTGGTCTACCCAGGGCTGCAAGCTGGTTGACACTAA
TAAAACTCGCACGACGTGTGCATGCAGCCACCTAACCAATTTTGCTATTCT
TCATGGCCCAACAGGGAAATTGTGTACAAAGATGGCGTCCACAAATTGCTG
CTGACAGTCATCACCTGGGTGGGCATCGTTGTCTCCCTCGTCTGCCTGGC
TATCTGCATCTTCACCTTCTGCTTCTTCCGAGGCCTGCAAAGCGACCGCA
ACACGATCCACAAGAACCTGTGTATCAACCTCTTCATCGCTGAGTTTATT
TTCCTAATAGGCATTGATAAAACACAGTACACGATTGCGTGCCCCGTGTT
TGCAGGACTCCTGCACCTTTTCTTCTTGGCTGCTTTTTCTGATGTGCC
TAGAAGGTGTGCAGCTCTACCTCATGTTGGTTGAAGTTTTTCGAGAGTGAA
TACTCAAGGAAGAAGTATTACTATGTGCGCGGGTACCTCTTCCCTGCCAC
AGTGGTTCGGTGTTTCAGCTGCTATCGACTACAAGAGTTACGGGACACTAG
AGGCTTGCTGGCTTCACGTTGATAACTATTTTCATATGGAGTTTCATTGGG
CCTGTTACTTTTCATCATTCTGCTAAATATTATTTTCTGGTGATCACGCT
GTGCAAAATGGTGAAACATTCAAACACTTTGAAACCAGATTCTAGCAGGT
TGGAAAACATTAAATAATTACCGTGTGTTGTGATGGATACTATAATACGGAC
TTACCTGGGTCTTGGGTGCTCGGTGCGTTCGCCCTGCTGTGTCTCCTGGG
CCTAACCTGGTTCCTTTGGGTGCTTTTTTGTAAACGAGGAGACCGTTGTCA
TGGCTTATCTCTTCACCGCCTTTAATGCTTTCCAGGGACTGTTTATTTTC
ATCTTCCACTGTGCTCTTCAAAGAAAGTACGGAAAGAGTATGCCAAGTG
CTTCAGACACTGGTACTGCTGTGGTGGCCTCCCGACCGAGAGCCCGCACA
GCTCTGTAAAGGCGTCCACCTCCCGCACCAGTGCTCGTTACTCCTCTGGT
ACACAGAGCCGTATAAGAAGGATGTGGAATGACACCGTGAGGAAGCAGTC
TGAATCGTCTTTTATCTCAGGTGACATCAATAGCACTTCTACCCTTAATC
AAGGAATGACTGGCAATTACCTACTAACAACCCCTCTTCTTCGACCCAC
GGCACTAACAACCCCTATAACACATTGCTCGCTGAAACAGTTGTATGTAA
TGCCCTTTCAGCGCCCGTGTTTAACTCACCAGGACATTCAGTGAACAATA
CCCGGGACACCCAGCGCCATGGATACTCTACCGCTAAATGGTAACTTCAAC
AACAGCTACTCCCTGCGCAAGGCCGACTACCACGACGGCGTGCAGGTTGT
GGACTGTGGACTAAGTCTGAACGACACCGCGTTTGAGAAAATGATCATT
CAGAGTTAGTGACAAACAACCTCCGGGGTAGCAACAAAACCCACAACCTG
GAGCTCAAGCTCCCAGTTAAACCCGTGATTGGCGGCAGCAGCAGCGAAGA

8/23

TGACGCGATCGTGGCCGACGCCTCATCTTTGATGCACGGTGATAAACCAG
GGCTGGAATTCCGCCACAAAGAGCTGGAGGCACCGCTCATCCCTCAGCGG
ACTCACTCGCTTCTGTACCAACCCAGAAAAAGTGAAACCCGAGGCAAC
CGACAGCTACGTCTCCAGCTGACGGCCGAGGCCGACGAGCACCTCCAGT
CCCCAACAGAGACTCTCTGTACACGAGCATGCCAACCTAAGAGACTCT
CCCTACCCGGAGAGCAGCCCGGACATGGCAGAGGACCTGTCTCCCTCCAG
GAGGAGCGAGAACGAGGACATTTACTACAAAAGTATGCCCAATCTTGGGG
CTGGCCGCCAGCTCCAGATGTGCTACCAGATCAGCAGAGGCAATAGCGAT
GGCTACATCATCCCCATTAACAAAGAAGGGTGCATCCCAGAGGGGGACGT
CAGGAAGGACAGATGCAGCTGGTAACAAGTCTTTAA

FIGURE 6d

Peptide sequences for YSG2 (SEQ ID No.10) (CIRL, rat)
CIRL-2 variant BC

MVSSGCRMRLWFMIIISFSPNTEGFSRAALPFGLVRRELSCEGYSIDLR
CPGSDVIMIESANYGRDDKICDADPFQMENTDCYLPDAFKIMTQRCNNR
TQCVVVTGSDVFPDPCPGTYKYLEVQYECVPYMEQKVFCPGTLKAI VDS
PSIYEAQKAGAWCKDPLQAADKIYFMPWTPYRTDTLIEYASLEDFQNSR
QTTTYKLPNRVDGTGFVVDGAVFFNKERTRNIVKFDLRTRIKSGEAI IN
YANYHDTSPYRWGGKTDIDLAVDENGLWVIYATEQNNGMIVISQLNPYTL
RFEATWETTYDKRAASNAFMICGVLYVVRSVYQDNESEAGKNVIDYIYNT
RLSRGEHVDVFPFNQYQYIAAVDYNPRDNQLYVWNNNFILRYSLEFGPPD
PAQVPTTAVTITSSAELFKTTVSTTSSTSQRGPVSSTVAGPQEGSRGTP
PPAVSTTKIPPVTNIFPLPERFCEALEMKGIKWPQTQRGMMVERPCPKGT
RGTASYLCMASTGTWNPKGPDLSNCTSHWVNQLAQKIRSGENAASLANEL
AKHTKGTVFAGDVSSSVRLMEQLVDILDAQLQELKPSEKDSAGRSYNKLQ
KREKTCRAYLKAI VDTVDNLLRAETLDCWKHMNSSEQAHTATMLLD TLEE
GAFVLADNLLLEPTRVSMPTDNIVLEVAVLSTEGQVQDFTFHLGFKGAFSS
IQLSANTVKQNSRNLAKVVFIIYRSLGPFLSTENATVKLGADLLGRNST
IAVNSHVLVSINKESSRVYLTDPVLF SMPHIDSDNYFNANCSFWNYSER
TMMGYWSTQGCKLVD TNKTRTTCACSHLTNFAILMAHREIVYKDG VHKLL
LTVITWVGIVVSLVCLAICIFTFCFFRGLQSDRNTIHKNL CINLFIAEFI
FLIGIDKTQYTIACPVFAGLLHFFFLAAFSWMCLEGVQLYLM LVEVFES
YSRKKYYYVAGYLF PATVVGVSAAIDYKSYGTLEACWLHVDNYFIWSFIG
PVTFIILLNII FLVITLCKMVKHSNTLKPDS SRLENINNYRVCDGYNTD
LPGSWVLGAFALLCLLGLTWSFGLLFVNEETVVMAYLFTAFNAFQGLFIF
IFHCALQKKVRKEYAKCFRHWYCCGGLPTESPHSSVKASTSRTSARYSSG
TQSRIRRMWNDTVRKQSESSFISGDINSTSTLNQGMTGNYLLTNPLLRPH
GTNNPYNTLLAETVVCNAPSAPVFNSPGHSLNNTRDTSAMDTLPLNGNFN
NSYSLRKADYHDGVQVVD CGLSLNDTAFEKMI ISELVHNNLRGSKNTHNL
ELKLPVKPVIGGSSSEDDAIVADASSLMHGDNPGLFRHKELEAPLIQR
THSLLYQPQKKVKPEATDSYVSQLTAEADEHLQSPNRDSLYTSMPNLRDS
PYPESSPDMAEDLSPSRRENEEDIYKSM PN LGAGRQLQMCYQISRGNSD
GYIIPINKEGCIPEGDVREGOMQLVTS L

9/23

FIGURE 6e

Gene sequences for YSG2 (SEQ ID No.11) (CIRL, rat)
CIRL-3 variant BA (other variants: AA, AB, AC, BB, BC)

ATGTGTCCACCTCAGCTGTTTCATCCTCATGATGCTTTTAGCACCTGTAGT
TCATGGTGGCAAGCACAAATGAGAGACATCCAGCCCTCGCTGCTCCACTGC
GACATGCTGAGCACAGCCCAGGAGGCCCTCTCCCTCCCAGACATCTTCTT
CAGCAGCCAGCTGCAGAGCGCTCTACAGCTCATCGAGGACAAGGGCCACG
TGGAAGTGCAGAGGAGTTCGCGGACCCGGTGCCCCAGGAGCACAGATTG
CAGCCCAAGCTTTCAGCCGTGCCCAATTCCCATGGCAGTGGTCCGCAGA
GAGCTCTCCTGTGAGAGCTACCCCATTTGAGCTACGCTGTCCAGGCACAGA
CGTCATCATGATCGAAAGCGCCAACTACGGGAGGACAGATGACAAGATCT
GTGACTCGGACCCTGCTCAGATGGAGAATATTCGGTGTTATCTGCCAGAT
GCCTATAAGATTATGTCTCAAAGATGCAATAACAGAACCCAGTGTGCAGT
GGTGGCAGGTCTTGATGTATTTCCAGACCCATGTCCGGGAACATATAAAT
ACCTTGAAGTGCAGTATGAATGTGTCCCTTACAAAGTGGAACAAAAGTT
TTTCTTTGTCCCGGACTGCTCAAAGGAGTGTACCAGAGCGAACACTTGT
TGAATCTGACCACCAATCTGGGGCATGGTGCAAAGACCCTCTACAGGCTT
CTGACAAGATTTACTATATGCCCTGGACTCCCTACAGAACCGATAACCCTG
ACAGAGTATTCATCCAAAGATGACTTCATTGCTGGAAGGCCGACAACCTAC
ATACAAGCTCCCTCACAGAGTGGATGGTACTGGATTTGTAGTATATGATG
GTGCCCTGTTCTTCAACAAGGAGCGTACAAGGAACATAGTAAAGTTTGAT
TTGAGGACTAGGATAAAGAGTGGAGAGGCAATCATAGCAAATGCTAACTA
CCATGATACCTCCCCATACCGATGGGGTGGCAAGTCCGACATAGACTTGG
CAGTGGATGAAAACGGATTATGGGTAATCTATGCAACAGAACAGAACAAAT
GGCAAAATTGTTATTAGCCAGTTGAACCCTTACACCCTACGGATTGAGGG
GACATGGGACACTGCCTATGATAAAAGGTCTGCTTCCAATGCATTTATGA
TTTGTGGGATTCTGTATGTGGTCAAGTCTGTATATGAGGATGACGACAAT
GAGGCCACCGGTAATAAGATTGACTACATTTACAATACTGACCAAAGCAA
GGATAGCCTGGTGGATGTACCCTTTCCCAACTCATACCAGTACATAGCAG
CCGTGGACTACAATCCCAGGGACAATCTGCTGTACGTGTGGAACAACCTAC
CATGTTGTCAAATACTCCTTGGACTTCGGGCCTCTGGATAGCAGATCAGG
GCCAGTGCATCATGGACAAGTTTCCTACATCTCTCCACCGATTACCTTG
ACTCTGACCTGGAAAGGCCCTGTGAGAGGGAATTTCTACCACAGGACCC
CTGGGTATGGGAAGCACGACCACCAGCACACCCTCCGGACTACCACCTG
GAACCTAGGGAGGAGTACAACGCCATCCTTGCCTGGCAGAAGAAACCGCA
GTACCAGTACGCCGTCCCCAGCGATTGAGGTGCTGGATGTTACCACACAC
CTGCCATCTGCAGCCTCCCAAATCCCAGCGATGGAAGAGAGCTGCGAGGC
TGTGGAAGCCCGAGAGATCATGTGGTTTAAGACCCGACAGGGGCAAGTAG
CAAAGCAGTCATGCCAGCAGGAACCATAGGTGTATCAACTTACCTGTGT
CTTGCTCCTGATGGAATATGGGATCCCCAAGGACCAGATCTCAGCAACTG
CTCTTCTCCTTGGGTCAATCACATAACACAGAAGCTGAAATCTGGAGAAA
CAGCTGCCAATATTGCCAGAGAGCTAGCAGAACAGACCAGAAATCATTTG
AACGCCGGGGATATCACCTACTCAGTTCGTGCCATGGACCAACTGGTTGG
CCTCCTGGACGTACAGCTCAGGAATTTGACACCAGGGGGGAAGGACAGTG
CTGCCCCAAGCTTGAACAAGCTTCAGAAAAGAGAGCGCTCTTGACAGAGCC
TATGTCCAGGCGATGGTGGAGACAGTTAACAATCTCCTTCAGCCACAAGC
TCTGAATGCGTGGAGGGACCTGACGACAAGTGATCAACTACGCGCAGCCA
CCATGTTGCTCGACACTGTGGAGGAGAGTGCTTTCGTGTTAGCCGATAAC

10/23

CTTTTGAAGACCGACATTGTCAGGGAGAATACAGACAATATTCAGTTGGA
GGTTGCAAGGCTGAGCACGGAAGGAAACCTAGAAGATCTAAAATTTCCAG
AAAACACGGGCCACGGAAGCACTATACAGCTTCCGCAAACACGTTAAAG
CAAAATGGCCGGAATGGAGAGATTAGAGTGGCCTTTGTCTGTATAACAA
CCTGGGTCCTTATTTATCTACGGAGAATGCCAGTATGAAGTTGGGCACAG
AAGCTATGTCCACAAATCACTCAGTTATCGTCAATTCCCCTGTTATTACA
GCAGCAATAAATAAGGAATTCAGTAATAAAGTGTATTTGGCTGATCCTGT
GGTATTTACTGTTAAACATATCAAGCAGTCAGAGGAAAATTTCAACCTA
ACTGTTCAATTTTGGAGCTATTCCAAGCGCACAATGACAGGTTATTGGTCA
ACACAAGGCTGTGACTCCTGACAACGAACAAGACACACACTACGTGCTC
CTGTAACCACCTCACCAACTTCGCAGTATTAATGGCACATGTGGAAGTTA
AGCACAGCGATGCCGTCCACGATCTTCTTCTGGATGTGATCACGTGGGTC
GGAATCCTGTTGTCTCTTGTCTCTCTGATCTGCATCTTCACATTCTG
CTTCTTCCGTGGGCTCCAGAGCGACCGTAACACCATTCACAAGAACCTGT
GCATCAGCCTGTTTGTGGCAGAACTGCTCTTCTGATTGGGATCAACAGA
ACCGACCAACCGATTGCCTGTGCAGTGTCTTGGGCTCTTTTGCATTTCTT
CTTCTTGGCGGCCTTCACCTGGA¹GTCTTCTAGAAGGGGTACAGCTGTATA
TCATGCTGGTGGAGGTCTTTGAGAGTGAGCATTCCCGTAGGAAGTACTTC
TATCTGGTTGGCTACGGGATGCCCCGACTCATCGTGGCCGTTTCTGCTGC
AGTCGACTACAGGAGCTATGGAACAGACAAAGTATGTTGGCTTCGCCTTG
ACACCTACTTCATTTGGAGTTTTATAGGACCAGCGACCTTGATAATTATG
CTGAATGTAATCTTCCTCGGGATTGCTTTATACAAAATGTTTCACCATAC
TGCCATACTGAAACCTGAATCAGGCTGTCTTGATAATATCAAGTCATGGG
TTATAGGTGCAATAGCGCTGCTCTGCCTATTAGGATTGACCTGGGCCTTT
GGACTCATGTATATTAATGAAAGCACAGTCATCATGGCGTATCTCTTCAC
CATTTTCAATTCTCTACAGGGGATGTTTATATTCATTTTCCACTGTGTCC
TACAGAAGAAGGTACGGAAGAGTATGGGAAATGCCTACGGACGCATTCG
TGTAGTGGGAAAAGCACGGAGAGTTCGATTGGCTCAGGGAAAACATCTGG
TTCTCGAACTCCAGGACGGTATTCCACAGGCTCACAGAGCCGGATTCCGA
GAATGTGGAATGACACCGTCCGAAAGCAGTCAGAGTCATCCTTCATCACT
GGAGACATAAACAGCTCAGCGTCGCTCAACAGAGAGGGGCTTCTGAACAA
TGCCAGGGATACAAGTGTGATGGATACTCTACCACTGAATGGTAACCATG
GCAACAGTTACAGCATTGCTGGCGGCGAATACCTGAGCAACTGTGTGCAA
ATTATAGACCGTGGCTATAACCACAACGAGACCGCCCTAGAAAAAAGAT
CCTAAAGGAACTCACTTCCAATAATATCCCTTCATACCTGAACAACACG
AGCGCTCCAGCGAACAGAACCGGAACATGATGAACAACTGGTGGACAAC
TTAGGCAGTGGGAGTGAAGATGACGCCATAGTCCTGGATGACGCAGCGTC
CTTTAACCACGAGGAGAGTCTGGGCTGGAACCTATTACGAGGAATCGG
ATGCTCCCTTGCTGCCCCGAGGGTTTACTCCACCGATAACCACCAGCCA
CACCATTACAGCAGGAGGCGGCTCCCCAGGACCACAGCGAGAGCTTCTT
CCCTCTGCTAACCAGCAGCACACAGAAGACCCGAGTCACCGCACAGGG
ACTCTCTGTACACCAGCATGCCGGCCCTGGCCGGTGTGCCCGCTGCAGAC
AGTGTGACCACCAGCACCCAGACCGAAGCCGAGCGGCCAAGGGTGGTGA
CGCCGAAGATGTTTACTACAAAAGCATGCCAAACCTGGGCTCCAGAAACC
ATGTGCACCCGCTGCACGCCTACTACCAGCTAGGGCGAGGCAGCAGCGAT
GGATTATAGTTCTTCCCAATAAAGATGGGGCCTCTCCGGAGGGGACTTC
CAAAGGACCGGCGCACTTGGTCACTAGTCTATAG

11/23

Figure 6f

Peptide sequences for YSG2 (SEQ ID No.12) (CIRL, rat).
CIRL-3 variant BA

MCPPQLFILMMLLAPVVHGGKHNERHPALAAPLRHAEHSPGGPLPPRHLL
QQPAAERSTAHRGQGPRGTARGVVRGPGAPGAQIAAQAFSRAPIPMAVVR
ELSCESYPIELRCPGTDVIMIESANYGRITDDKICDSDPAQMENIRCYLPD
AYKIMSQRCCNNRTQCAVVAGPDVFPDPCPGTYKYLEVQYECVPYKVEQKV
FLCPGLLKGVYQSEHLFESDHQSGAWCKDPLQASDKIYYMPWTPYRTDTL
TEYSSKDDFIAGRPTTTYKLPHRVDGTGFVVYDGFALFFNKERTRNIVKFD
LRTRIKSGEAIANANYHDTSPYRWGGKSDIDLAVDENGWLWVIYATEQNN
GKIVISQLNPYTLRIEGTWDATYDKRSASNAFMICGILYVVKSVYEDDDN
EATGNKIDYIYNTDQSKDSLVDVFPNSYQYIAAVDYNPRDNLLYVWNNY
HVVKYSLDFGPLDSRSGPVHHGQVSYISPPHLDSDLERPPVRGISTTGP
LGMGSTTTTTLRTTTWNLGRSTTPSLPGRNRSTSTPSAIEVLDVTTH
LPSAASQIPAMEESCEAVEAREIMWFKTRQGQVAKQSCPAGTIGVSTYLC
LAPDGIWDPQGPDLNSCSPWVNHTQKLKSGETAANIARELAEQTRNHL
NAGDITYSVRAMDQLVGLLDVQLRNLTPGGKDSAARSLNKLQKRERSRA
YVQAMVETVNNLLQPQALNAWRDLTSDQLRAATMLLDTVEESAFVLADN
LLKTDIVRENTDNIQLEVARLSTEGNLEDLKFPEENTGHGSTIQLSANTLK
QNGRNGEIRVAFVLYNNLGPYLSTENASMKLGTEAMSTNHSVIVNSPVIT
AAINKEFSNKVYLADPVVFTVKHIKQSEENFNPNCSFWSYSKRMTMTGYWS
TQGCRLTTNKTHHTTCSNHLTNFAVLMAHVEVKHSDAVHDLDDLVDITWV
GILLSLVCLLICIFTFCFFRGLQSDRNTIHKNLCSLFFVAELLFLIGINR
TDQPIACAVFAALLHFFFLAAFTWMFLEGVQLYIMLVEVFESHSRRKYF
YLVGYGMPALIVAVSAAVDYRSYGTDKVCWLRLDTYFIWSFIGPATLIIM
LNVIFLGIALYKMFHHTAILKPESGCLDNKSWVIGAIALLCLLGLTWAF
GLMYINESTVIMAYLFTIFNSLQGMFIFIFHCVLQKKVRKEYGKCLRTHC
CSGKSTESSIGSGKTSGSRTPGRYSTGSQSRIRRMWNDTVRKQSESSFIT
GDINSSASLNREGLLNARDTSVMDTLPLNGNHGNSYSIAGGEYLSNCVQ
IIDRGYNHNETALEKKILKELTSNYIPSYLNNHERSSEQNRNMMNKLVDN
LGSGSEDDAIVLDDAASFNHEESLGLLELIHEESDAPLLPPRVYSTDNHQP
HHYSRRRLPQDHSESFPLLTDEHTEDPQSPHRDSLYTSMPALAGVPAAD
SVTTSTQTEAAAAGGDAEDVYKSMPLGSRNHVHPLHAYYQLGRGSSD
GFIVPPNKDGASPEGTSKGPAPHLVTSL

FIGURE 7a

Gene sequence for YSG 5 (SEQ ID No.13) (TRK E, human)

GAGAGATGCTGCCCCACCCCCTTAGGCCCCGAGGGATCAGGAGCTATGGGACCAGAGGCC
CTGTCATCTTTACTGCTGCTGCTCTTGGTGGCAAGTGGAGATGCTGACATGAAGGGACAT
TTTGATCCTGCCAAGTGCCGCTATGCCCTGGGCATGCAGGACCGGACCATCCCAGACAGT
GACATCTCTGCTTCCAGCTCCTGGTCAGATTCCACTGCCGCCCCGCCACAGCAGGTTGGAG
AGCAGTGACGGGGATGGGGCCTGGTGCCCCGAGGGTTCGGTGTTTCCCAAGGAGGAGGAG
TACTTGCAGGTGGATCTACAACGACTCCACCTGGTGGCTCTGGTGGGCACCCAGGGACGG
CATGCCGGGGGCTGGGCAAGGAGTTCTCCCGGAGCTACCGGCTGCGTTACTCCCGGGAT
GGTCGCCGCTGGATGGGCTGGAAGGACCGCTGGGGTCAGGAGGTGATCTCAGGCAATGAG
GACCCTGAGGGAGTGGTGCTGAAGGACCTTGGGCCCCCATGGTTGCCCGACTGGTTTCGC

12/23

TTCTACCCCCGGGCTGACCGGGTCATGAGTGTCTGTCTGCGGGTAGAGCTCTATGGCTGC
CTCTGGAGGGATGGACTCCTGTCTTACACCGCCCCCTGTGGGGCAGACAATGTATTTATCT
GAGGCCGTGTACCTCAACGACTCCACCTATGACGGACATACCGTGGGCGGACTGCAGTAT
GGGGGTCTGGGCCAGCTGGCAGATGGTGTGGTGGGGCTGGATGACTTTAGGAAGAGTCAG
GAGCTGCGGGTCTGGCCAGGCTATGACTATGTGGGATGGAGCAACCACAGCTTCTCCAGT
GGCTATGTGGAGATGGAGTTTGAGTTTGACCGGCTGAGGGCCTTCCAGGCTATGCAGGTC
CACTGTAACAACATGCACACGCTGGGAGCCCGTCTGCCTGGCGGGGTGGAATGTCGCTTC
CGGCGTGGCCCTGCCATGGCCTGGGAGGGGGAGCCCATGCGCCACAACCTAGGGGGC AAC
CTGGGGGACCCAGAGCCCGGGCTGTCTCAGTGCCCCCTTGGCGGCCGTGTGGCTCGCTTT
CTGCAGTGCCGCTTCCTCTTTGCGGGGCCCTGGTTACTCTTCAGCGAAATCTCCTTCATC
TCTGATGTGGTGAACAATTCCTCTCCGGCACTGGGAGGCACCTTCCCGCCAGCCCCCTGG
TGGCCGCTGGCCACCTCCCACCAACTTCAGCAGCTTGGAGCTGGAGCCCAGAGGCCAG
CAGCCCGTGGCCAAGGCCGAGGGGAGCCCGACCGCCATCCTCATCGGCTGCCTGGTGGCC
ATCATCCTGCTCCTGCTGCTCATCATTGCCCTCATGCTCTGGCGGCTGCACTGGCGCAGG
CTCCTCAGCAAGGCTGAACGGAGGGTGTGGAAGAGGAGCTGACGGTTACCTCTCTGTCT
CCTGGGGACACTATCCTCATCAACAACCGCCCAGGTCTAGAGAGCCACCCCGTACCAG
GAGCCCCGGCCTCGTGGGAATCCGCCCCACTCCGCTCCCTGTGTCCCCAATGGCTCTGCC
TACAGTGGGGACTATATGGAGCCTGAGAAGCCAGGCGCCCCGCTTCTGCCCCACCTCCC
CAGAACAGCGTCCCCATTATGCCGAGGCTGACATTGTTACCCTGCAGGGCGTACCCGGG
GGCAACACCTATGCTGTGCCTGCACTGCCCCCAGGGGCAGTCGGGGATGGGCCCCCAGA
GTGGATTTCCCTCGATCTCGACTCCGCTTCAAGGAGAAGCTTGGCGAGGGCCAGTTTGGG
GAGGTGCACCTGTGTGAGGTCGACAGCCCTCAAGATCTGGTCAGTCTTGATTTCCTCCTT
AATGTGCGTAAGGGACACCTTTTGCTGGTAGCTGTCAAGATCTTACGGCCAGATGCCACC
AAGAATGCCAGGAATGATTTCTGAAAGAGGTGAAGATCATGTGAGGCTCAAGGACCCA
AACATCATTCGGCTGCTGGGCGTGTGTGTGCAGGACGACCCCTCTGCATGATTACTGAC
TACATGGAGAACGGCGACCTCAACCAGTTCTCAGTGCCCCACCAGCTGGAGGACAAGGCA
GCCGAGGGGGCCCCCTGGGGACGGGCAGGCTGCGCAGGGGCCCCACCATCAGCTACCCAATG
CTGCTGCATGTGGCAGCCCAGATCGCCTCCGGCATGCGCTATCTAGCCACACTCAACTTT
GTACATCGGGACCTGGCCACGCGGAACCTGCCTAGTTGGGGAAAATTTACCATCAAAATC
GCAGACTTTTGGCATGAGCCGGAACCTCTATGCTGGGGACTATTACCGTGTGCAGGGCCGG
GCAGTGCTGCCCATCCGCTGGATGGCCTGGGAGTGATCCTCATGGGGAAGTTCACGACT
GCGAGTGACGTGTGGGCCTTTGGTGTGACCCTGTGGGAGGTGCTGATGCTCTGTAGGGCC
CAGCCCTTTGGGCAGCTCACCGACGAGCAGGTTCATCGAGAACGCGGGGGAGTTCTTCCGG
GACCAGGGCCGGCAGGTGTACCTGTCCCGGCCGCTGCCTGCCCCGAGGGCCTATATGAG
CTGATGCTTCGGTGCTGGAGCCGGGAGTCTGAGCAGCGACCACCCTTTTCCCAGCTGCAT
CGGTTCCTGGCAGAGGATGCACTCAACACGGTGTGAATCACACATCCAGCTGCCCCCTCCC
TCAGGGAGTGATCCAGGGGAAGCCAGTGACACTAAAACAAGAGGACACAATGGCACCTCT
GCCCTTCCCCTCCCGACAGCCCATCACCTCTAATAGAGGCAGTGAGACTGCAGGTGGGCT
GGGCCCCACCCAGGGAGCTGATGCCCCCTTCTCCCCCTTCTGACACACTCTCATGTCCCCCT
TCCTGTTCTTCTTCTTAGAAGCCCCCTGTGCCCCACCCAGCTGGTCCTGTGGATGGGATC
CTCTCCACCCTCCTCTAGCCATCCCTTGGGGAAGGGTGGGGAGAAATATAGGATAGACAC
TGGACATGGCCCATTTGGAGCACCTGGGCCCCACTGGACAACACTGATTCCTGGAGAGGTG
GCTGCGCCCCCAGCTTCTCTCTCCCTGTACACACTGGACCCCACTGGCTGAGAATCTGG
GGGTGAGGAGGACAAGAAGGAGAGGAAAATGTTTCTTGTGCTGCTCCTGTACTTGTCC
TCAGCTTGGGCTTCTTCTCCTCCATCACCTGAAACACTGGACCTGGGGGTAGCCCCGCC
CCAGCCCTCAGTCACCCCCACTTCCCACCTGCAGTCTTGTAGCTAGAACTTCTCTAAGCC
TATACGTTTCTGTGGAGTAAATATTGGGATTGGGGGGAAAGAGGGAGCAACGGCCCATAG
CCTTGGGGTTGGACATCTCTAGTGTAGCTGCCACATTGATTTTTCTATAATCACTTGGGG
TTTGTACATTTTGGGGGGAGAGACACAGATTTTTTACACTAATATATGACCTAGCTTGA

13/23

GGCAATTTTAATCCCCTGCACTAGGCAGGTAATAATAAAGGTTGAGTTTTCCACAAAAAA
AAAAAAAAAAAAAA

Figure 7b

Peptide sequence for YSG 5 (SEQ ID No.14) (TRK E, human)

MGPEALSSLLLLLLVASGDADMKGHFDPAKCRYALGMQDR TIPDS DISASSSWSDSTAAR
HSRLESSDGDGAWCPAGSVFPKEEY LQVDLQRLHLVALVGTQGRHAGGLGKEFSRSYRL
RYSRDGRRWMGWKDRWGQEVISGNEDEPGVVLKDLGPPMVARLVRFYPRADRVMSVCLRV
ELYGCLWRDGLLSYTAPVGQTMYLSEAVYLNDSTYDGHTVGG LQYGG LGQLADGVVGLDD
FRKSQELRVWPGYDYVGWSNHSFSSGYVEMEF EFDR LRAFQAMQVHCNNMHTLGARLPGG
VECRFRRG PAMAWEGEPMRHNLGGNLGDPRARAVSVPLGGRVARFLQCRFLFAGPWLLFS
EISFISDVVNSSPALGGTFPPAPWWPPGPPPTNFSSLELEPRGQOPVAKAEGSPTAILI
GCLVAII LLLLLLIIALMLWRLHWRLLSKAERRVLEEEELTVHLSVPGDTILINNRPGPRE
PPPYQEPRPRGNPPHSAPCVPNGSAYS GDYMEPEKPGAPLLPPPQNSVPHYAEADIVTL
QGV TGGNTYAVPALPPGAVGDGPPRVDFPRSRLRFKEKLGE GQFGEVHLCEVDS PQDLVS
LDFPLNVRKGHPLLVAVKILRPDATKNARND FLKEVKIMSRLKDPNI IRL LGVCVQDDPL
CMITDYMENGDLNQFLSAHQLEDKAAEGAPGDGQAAQGP TISYPMLLHVAAQIASGMRYL
ATLNFVHRDLATRNCLVGENFTIKIADFGMSRNLYAGDY YRVQGRAVLPIRWMAWECILM
GKFTTASDVWAFGVTLWEVLMLCRAQPF GQLTDEQVIENAGEFFRDQGRQVYLSRPPACP
QGLYELMLRCWSRESEQRPPFSQLHRFLAEDALNTV

FIGURE 8a

Gene sequence for YSG7 (SEQ ID No.15) (UNC5H1, rat)

ATGGCCGTCCGGCCCCGGCCTGTGGCCAGTGCTCCTGGGCATAGTCCTCGCCGCCTGGCTT
CGTGGTTTCGGGTGCCCAGCAGAGTGCCACGGTGGCCAATCCAGTGCCCGGTGCCAACCCC
GACCTGCTGCCCCACTTCTGGTAGAGCCTGAGGACGTGTACATTGTCAAGAACAAAGCCG
GTGTTGTTGGTGTGCAAGGCTGTGCCTGCCACCCAGATCTTCTTCAAGTGCAATGGGGAA
TGGGTCCGCCAGGTGATCACGTAATTGAACGCAGCACCGACAGCAGCAGCGGATTGCCA
ACCATGGAGGTCCGTATCAACGTATCGAGGCAGCAGGTAGAGAAAGTGTTTGGGCTGGAG
GAATACTGGTGCCAGTGTGTGGCATGGAGCTCCTCGGGTACCACCAAAGTCAGAAGGCC
TACATCCGGATTGCCTATTTGCGCAAGAACTTTGAGCAGGAGCCACTGGCCAAGGAAGTG
TCACTGGAGCAAGGCATTGTACTACCTTGTGCCCCCAGAAGGAATCCCCCAGCTGAG
GTGGAGTGGCTTCGAAATGAGGACCTCGTGGACCCCTCCCTCGATCCCAATGTGTACATC
ACGCGGGAGCACAGCCTAGTCGTGCGTCAGGCCCGCCTGGCCGACACGGCCAACCTACACC
TGTGTGGCCAAGAACATCGTAGCCCGTCGCCGAAGCACCTCTGCAGCGGTCAATTGTTTAT
GTGAACGGTGGGTGGTTCGACGTGGACTGAGTGGTCCGTCTGCAGCGCCAGCTGTGGGCGT
GGCTGGCAGAAACGGAGCCGGAGCTGCACCAACCCGGCACCTCTCAACGGGGGCGCCTTC
TGTGAGGGGCAGAATGTCCAGAAAACAGCCTGCGCCACTCTGTGCCCAGTGGATGGGAGC
TGGAGTTCGTGGAGTAAGTGGTCAGCCTGTGGGCTTGACTGCACCCACTGGCGGAGCCGC
GAGTGCTCTGACCCAGCACCCCGCAATGGAGGTGAGGAGTGTGCGGGTGCTGACCTGGAC
ACCCGCAACTGTACCAAGTGACCTCTGCCTGCACACCGCTTCTTGCCCCGAGGACGTGGCT
CTCTACATCGGCCTTGTGCTGTGGCTGTGTGCCTCTTCTTGCTGTGCTGGCCCTTGGA
CTCATTTACTGTGCGAAGAAGGAAGGGCTGGACTCCGATGTGGCCGACTCGTCCATCCTC
ACCTCGGGCTTCCAGCCTGTGACGATCAAGCCCAGCAAAGCAGACAACCCCCACCTGCTC
ACCATCCAGCCAGACCTCAGCACCACTACCACTACCAGGGCAGTCTATGTTTCGAGG

CAGGATGGACCCAGCCCCAAGTTCCAGCTCTCTAATGGTCACCTGCTCAGCCCCTGGGG
AGTGGCCGCCATACGTTGCACCACAGCTCACCACCTCTGAGGCTGAGGACTTCGTCTCC
CGCCTCTCCACCCAAACTACTTTTCGTTCCCTGCCCCGCGGCACCAGCAACATGGCCTAC
GGGACCTTCAACTTCCTCGGGGGCCGGCTGATGATCCCTAATACGGGGATCAGCCTCCTC
ATACCCCCGGATGCCATCCCCGAGGAAAGATCTACGAGATCTACCTCACACTGCACAAG
CCAGAAGACGTGAGGTTGCCCTAGCTGGCTGTCAGACCCTGCTGAGTCCAGTTCGTTAGC
TGTGGGCCCCCAGGAGTCTGCTCACC CGCCAGTCATCCTTGCAATGGACCACTGTGGA
GAGCCAGCCCTGACAGCTGGAGTCTGCGCCTCAAAAAGCAGTCCTGCGAGGGCAGTTGG
GAGGATGTGCTGCACCTTGTTGAGGAGTCACCTTCCACCTCTACTACTGCCAGCTGGAG
GCCGGGGCCTGCTATGTCTTCACGGAGCAGCTGGGCCGCTTTGCCCTGGTAGGAGAGGCC
CTCAGCGTGGCTGCCACCAAGCGCCTCAGGCTCCTTCTGTTTGCTCCCGTGGCCTGTACG
TCCCTTGAGTACAACATCCGAGTGTACTGCCTACACGACACCCACGACGCTCTCAAGGAG
GTGGTGCAGCTGGAGAAGCAGCTAGGTGGACAGCTGATCCAGGAGCCTCGCGTCTGAC
TTCAAAGACAGTTACCACAACCTACGTCTCTCCATCCACGACGTGCCAGCTCCCTGTGG
AAGAGCAAGCTACTTGTGCTAGCTACCAGGAGATCCCTTTTTTACCACATCTGGAACGGCACC
CAGCAGTATCTGCACTGCACCTTCAACCCTGGAGCGCATCAACGCCAGCACCAGCGACCTG
GCCTGCAAGGTGTGGGTGTGGCAGGTGGAGGGAGATGGGCAGAGCTTCAACATCAACTTC
AACATCACTAAGGACACAAGGTTTGTGAATTGTTGGCTCTGGAGAGTGAAGGGGGGGTTC
CCAGCCCTGGTGGGCCCCAGTGCCTTCAAGATCCCCCTTCTCATTTCGGCAAAGATCATC
GCCAGTCTGGACCCACCCTGCAGCCGGGGCGCCGACTGGAGAACTCTAGCCCAGAACTT
CACCTGGACAGCCATCTTAGCTTCTTTGCCTCCAAGCCCAGCCCTACAGCCATGATCCTC
AACCTATGGGAGGCACGGCACTTCCCCAACGGCAACCTCGGCCAGCTGGCAGCAGCTGTG
GCCGGA CTGGGCCAACCAGATGCTGGCCTCTTACAGGTGTCGGAGGCCGAGTGTTGA

Figure 8b

Peptide sequence for YSG7 (SEQ ID No.16) (UNC5H1, rat)

MAVRPGLWPVLLGIVLAAWLRGSGAQQSATVANPVPGANPDLLPHFLVEPEDVYIVKNKP
VLLVCKAVPATQIFFKCNGEWVRQVDHVIERSTDSSSGLPTMEVRINVSRRQVEKVFGL
EYWCQCVAWSSSGTTKSQKAYIRIAYLRKNFEQEPLAKEVSLEQGIVLPCRPPGIPPAE
VEWLRNEDLVDPSLDPNVYITREHSLVVRQARLADTANYTCVAKNIVARRRSTSAIVY
VNGGWSTWTEWSVCSASCGRGWQKRSRSCNTPAPLNGGAFCEGQNVQKTACATLCPVDGS
WSSWSKWSACGLDCTHWSRECSDPAPRNGGEECRGADLDTRNCTSDLCLHTASCPEDVA
LYIGLVAVAVCLFLLLLALGLIYCRKKEGLSDVADSSILTS GFQPVSIKPSKADNP HLL
TIQPD LSTTTTTTYQGS LCSRQDGSPK FQLSNGHLLSPLGSGRHTLHHSSPTSEAEDFVS
RLSTQNYFRSLPRGTSNMAYGT FNFLGGRLMI PNTGISLLIPPDAI PRGKIYEIYLT LHK
PEDVRLPLAGCQTLLSPVSCGPPGVLLTRPVILAMDHCEPSPDSWSLRLKKQSCEGSW
EDVLHLGEESPSHLYYCQLEAGACYVFTEQLGRFALVGEALSVAATKRLRLLLFAPVACT
SLEYNIRVYCLHDTHDALKEVVQLEKQLGGQLIQEPRVLHFKDSYHNLRLSIHDPSSLW
KSKLLVSYQEIPFYHIWNGTQQYLHCTFTLERINASTSDLACKVWVWQVEGDGQSFNINF
NITK DTRFAELLALESEGGVPALVGPSAFKI PFLIRQKI IASLDPPCSR GADWRTLAQKL
HLDSHLSFFASKPSPTAMILNLWEARHFPNGNLGQLAAAVAGLGQPDAGLFTVSEAE C

15/23

FIGURE 9a

Gene sequences for YSG8 (SEQ ID No.17)

(synapsin I, rat) Synapsin IA

ATGAACTACCTGCGGCGCCGCTGTCTGGACAGCAACTTCATGGCCAATCT
GCCTAATGGGTATATGACAGACCTGCAGCGCCCGCAACCACCTCCGCGCG
CGCCCTCAGCCGCCAGCCCAGGGGGCCACTCCCAGGATCCGCTGCTGCCTCT
GCTGAGAGGGCCTCCACAGCTGCTCCAGTGGCCTCTCCAGCAGCCCCTAG
TCCCGGGTCTCTCGGGGGGCGGTGGCTTCTTCTCCTCGCTGTCTAACGCGG
TCAAACAGACCACAGCAGCTGCAGCCGCCACCTTCAGTGAGCAGGTGGGC
GGTGGCTCTGGGGGGCGCAGGCCGCGGGGGCGCCGCCAGGGTGCTGCT
GGTCATCGACGAGCCGCAACACCGACTGGGCAAAATACTTCAAAGGGAAGA
AGATCCATGGAGAAATTGACATTAAAGTAGAGCAAGCTGAATTCTCCGAT
CTCAATCTTGTGGCTCATGCCAATGGTGGATTCTCCGTGGACATGGAAGT
TCTTCGGAATGGGGTCAAAGTTGTGAGGTCTCTGAAGCCAGACTTTGTGC
TGATCCGCCAGCATGCCTTCAGCATGGCACGTAATGGAGACTACCGCAGT
TTGGTCATTGGGCTGCAGTATGCTGGGATCCCAGTGTTAACTCTTTGCA
TTCTGTCTACAACCTTTTGTGACAAACCCTGGGTGTTTGCCAGATGGTTC
GACTACACAAGAAGCTTGGAACAGAGGAATTCCTCTGATTGATCAGACT
TTCTATCCCAATCATAAAGAGATGCTCAGCAGCACAAACATACCCTGTAGT
TGTGAAGATGGGCCACGCACACTCTGGGATGGGCAAGGTCAAGGTAGACA
ACCAACATGACTTCCAGGATATTGCAAGTGTTGTGGCACTGACTAAGACA
TATGCCACTGCTGAGCCCTTCATTGATGCTAAATACGATGTGCGTGTCCA
GAAGATTGGGCAGAACTACAAGGCCTACATGAGGACATCAGTGTGAGGGA
ACTGGAAGACCAATACAGGCTCTGCTATGCTTGAGCAGATTGCTATGTCT
GACAGGTACAAGTTGTGGGTAGACACGTGCTCAGAGATTTTTGGGGGACT
TGACATCTGCGCAGTGGAAGCACTGCATGGCAAGGACGGAAGGGATCACA
TTATTGAGGTGGTGGGCTCCTCCATGCCACTCATTGGGGATCACCAGGAT
GAAGACAAGCAGCTCATCGTGGAACCTGTGGTCAACAAGATGACTCAGGC
TCTGCCCTCGGCAGCGGGATGCTTCCCCTGGCAGGGGTTCACACAGCCAGA
CTCCATCCCCAGGAGCCCTGCCCTTGGGCCGCCAGACCTCCCAGCAGCCT
GCAGGACCTCCTGCTCAACAACGACCCCCACCCAGGGAGGCCCTCCACA
ACCAGGCCCCAGGACCTCAGCGCCAGGGACCCCCGCTGCAACAGCGCCAC
CCCCACAAGGCCAGCAACATCTTTCTGGCCTTGGACCCCCAGCTGGCAGC
CCTCTGCCCCAGCGCCTACCAAGTCCCACAGCAGCACCTCAGCAGTCCGC
CTCTCAGGCCACACCAATGACCCAGGGTCAAGGCCGCCAGTCACGGCCAG
TGGCAGGAGGCCCGGAGCACCTCCAGCAGCCCGCCCGCCGGCCTCCCCA
TCTCCACAGCGTCAGGCAGGGCCCCCACAGGCTACCCGTCAGGCATCTAT
CTCTGGTCCAGCTCCACCGAAGGTCTCAGGAGCCTCACCCGGAGGGCAGC
AGCGCCAAGGCCCTCCCCAGAAACCCCCAGGCCCTGCTGGTCCCATTTCGT
CAGGCCAGCCAGGCAGGTCCCGGACCTCGCACTGGGGCCACCCACCACACA
GCAGCCCCGGCCAGCGGCCAGGTCTGCTGGACGTCCCACCAAACCAC
AGCTGGCTCAGAAACCCAGCCAGGATGTGCCACCACCCATCATTGCTGCT
GCCGGGGGACCCCCGACCCCCAGCTCAACAAATCCCAGTCTCTGACCAA
TGCTTCAACCTTCAGAGCCAGCCCCGCCAGGCCAGCCTTAGCCAGG
ATGAGGTGAAAGCTGAGACCATCCGCAGCCTGAGGAAGTCTTTCGCCAGC
CTCTTCTCCGACTGA

16/23

Figure 9b

Peptide sequence for YSG8 (SEQ ID No.18)
(synapsin I, rat) Synapsin IA

MNYLRRRLSDSNFMANLPNGYMTDLQRPQPPPPPPSAASPGATPGSAAAS
AERASTAAPVASPAAPSPGSSGGGGFFSSLSNAVKQTTAAAAATFSEQVG
GGSGGAGRGGAAARVLLVIDEPHTDWAKYFKGKKIHGEIDIKVEQAEFSD
LNLVAHANGGFSVDMEVLRNGVKVVRSLKPDFVLIRQHAFSMARNGDYRS
LVIGLQYAGIPSVNSLHSVNFCDKPWFVAQMVRLHKKLGTEEFPLIDQT
FYPNHKEMLSSTTYPVVVKMGHAHSGMGKVVDNQHDFQDIASVVALTKT
YATAEPFIDAKYDVRVQKIGQNYKAYMRTSVSGNWKTNTGSAMLEQIAMS
DRYKLWVDTCEIFGGLDICAVEALHGKDGRDHIIEVVGSSMPLIGDHQD
EDKQLLIVELVVNKMTQALPRORDASPGRGSHSQTPSPGALPLGRQTSQQP
AGPPAQQRPPPPQGGPPQPGPGPQROGPPLOQRPPPPQGGQHLGLGPPAGS
PLPQRLPSPTAAPQOSASQATPMTQGQGRQSRPVAGGPGAPPAARPPASP
SPQRQAGPPQATRQASISGPAPPKVS GASPGGQQRQGGPPQKPPGPAGPIR
QASQAGPGPRTGPPTTQQPRPSGPGPAGRPTKPQLAQKPSQDVPPIIAA
AGGPPHPQLNKSQSLTNAFNLPEPAPPRPSLSQDEVKAETIRSLRKSFAS
LFSD

Figure 9c

Gene sequences for YSG8 (SEQ ID No.19)
(synapsin I, rat) Synapsin IB

ATGAACTACCTGCGGCGCCGCTGTCTCGGACAGCAACTTCATGGCCAATCT
GCCTAATGGGTATATGACAGACCTGCAGCGCCCGCAACCACCTCCGCCGC
CGCCCTCAGCCGCCAGCCAGGGGCCACTCCCGGATCCGCTGCTGCCTCT
GCTGAGAGGGCCTCCACAGCTGCTCCAGTGGCCTCTCCAGCAGCCCCTAG
TCCCGGGTCTCTCGGGGGGCGGTGGCTTCTTCTCCTCGCTGTCTAACGCGG
TCAAACAGACCACAGCAGCTGCAGCCGCCACCTTCAGTGAGCAGGTGGGC
GGTGGCTCTGGGGGCGCAGGCCGCGGGGGCGCCGCCAGGGTGCTGCT
GGTCATCGACGAGCCGCACACCGACTGGGCAAAATACTTCAAAGGGAAGA
AGATCCATGGAGAAATTGACATTAAAGTAGAGCAAGCTGAATTCTCCGAT
CTCAATCTTGTGGCTCATGCCAATGGTGGATTCTCCGTGGACATGGAAGT
TCTTCGGAATGGGGTCAAAGTTGTGAGGTCTCTGAAGCCAGACTTTGTGC
TGATCCGCCAGCATGCCCTTCAGCATGGCACGTAATGGAGACTACCGCAGT
TTGGTCATTGGGCTGCAGTATGCTGGGATCCCCAGTGTTAACTCTTTGCA
TTCTGTCTACAACTTTTGTGACAAACCCTGGGTGTTTGCCCAGATGGTTC
GACTACACAAGAAGCTTGGAACAGAGGAATTCCCTCTGATTGATCAGACT
TTCTATCCCAATCATAAAGAGATGCTCAGCAGCACAAACATACCCTGTAGT
TGTGAAGATGGGCCACGCACACTCTGGGATGGGCAAGGTCAAGGTAGACA
ACCAACATGACTTCCAGGATATTGCAAGTGTGTGGCACTGACTAAGACA
TATGCCACTGCTGAGCCCTTCATTGATGCTAAATACGATGTGCGTGTCCA
GAAGATTGGGCAGAACTACAAGGCCTACATGAGGACATCAGTGTCAGGGA
ACTGGAAGACCAATACAGGCTCTGCTATGCTTGAGCAGATTGCTATGTCT
GACAGGTACAAGTTGTGGGTAGACACGTGCTCAGAGATTTTGGGGGACT
TGACATCTGCGCAGTGAAGCACTGCATGGCAAGGACGGAAGGGATCACA
TTATTGAGGTGGTGGGCTCCTCCATGCCACTCATTGGGGATCACCAGGAT

17/23

GAAGACAAGCAGCTCATCGTGGAACCTTGTGGTCAACAAGATGACTCAGGC
TCTGCCTCGGCAGCGGGATGCTTCCCCTGGCAGGGGTTCCACAGCCAGA
CTCCATCCCCAGGAGCCCTGCCCTTGGGCGCCAGACCTCCCAGCAGCCT
GCAGGACCTCCTGCTCAACAACGACCCCCACCCCAGGGAGGCCCTCCACA
ACCAGGCCCAGGACCTCAGCGCCAGGGACCCCCGCTGCAACAGCGCCAC
CCCCACAAGGCCAGCAACATCTTTCTGGCCTTGGACCCCCAGCTGGCAGC
CCTCTGCCCCAGCGCCTACCAAGTCCCACAGCAGCACCTCAGCAGTCCGC
CTCTCAGGCCACACCAATGACCCAGGGTCAAGGCCGCCAGTCACGGCCAG
TGGCAGGAGGCCCCGGAGCACCTCCAGCAGCCCGCCCGCCGGCCTCCCCA
TCTCCACAGCGTCAGGCAGGGCCCCCACAGGCTACCCGTCAGGCATCTAT
CTCTGGTCCAGCTCCACCGAAGGTCTCAGGAGCCTCACCCGGAGGGCAGC
AGCGCCAAGGCCCTCCCCAGAAACCCCCAGGCCCTGCTGGTCCCATTCTGT
CAGGCCAGCCAGGCAGGTCCCGGACCTCGCACTGGGCCACCCACCACACA
GCAGCCCCCGGCCAGCGGCCCAGGTCTGCTGGACGTCCCACCAAACCAC
AGCTGGCTCAGAAACCCAGCCAGGATGTGCCACCACCCATCATTGCTGCT
GCCGGGGGACCCCCGCACCCCCAGCTCAAAGCCAGCCCCGCCAGGCCCA
GCCTTAG

Figure 9d

Peptide sequence for YSG8 (SEQ ID No.20)
(synapsin I, rat) Synapsin IB

MNYLRRRLSDSNFMANLPNGYMTDLQRPQPPPPPSAASPGATPGSAAAS
AERASTAAPVASPAAPSPGSSGGGGFFSSLSNAVKQTAAAAATFSEQVG
GGSGGAGRGGAARVLLVIDEPHTDWAKYFKGKKIHGEIDIKVEQAEFS
LNLVAHANGGFSVDMEVLRNGVKVVRSLKPDFVLIRQHAFSMARNGDYRS
LVIGLQYAGIPSVNSLHSVYNFCDKPWVFAQMVRHLHKKLGTEEFPLIDQT
FYPNHKEMLSSTTYPVVVKMGHAHSGMGKVVDNQHDFQDIASVVALTKT
YATAEPFIDAKYDVRVQKIGQNYKAYMRTSVSGNWKNTTGSAMLEQIAMS
DRYKLWVDTCEIFGGLDICAVEALHGKDGDRDHIIEVVGSSMPLIGDHQD
EDKQLLIVELVNVKMTQALPRQORDASPRGSHSQTSPGALPLGRQTSQQP
AGPPAQQRPPPQGGPPQPGPGPQROGPPLQQRPPPQGGHLSGLGPPAGS
PLPQRLPSPTAAPQQSASQATPMTQGQGRQSRPVAGGPGAPPAARPPASP
SPQRQAGPPQATROASISGPAPPKVSASPGGQQRQGPQKPPGPAGPIR
QASQAGPGPRTGPPTTQQPRPSGPGPAGRPTKPQLAQKPSQDVPPPIIAA
AGGPPHPQLKASPAQAQP

FIGURE 10a

Gene sequence for YSG10 (SEQ ID No. 21) (TNF-alpha, rat)

ATGAGCACAGAAAGCATGATCCGAGATGTGGAACCTGGCAGAGGAGGCGCTCCCCAAAAAG
ATGGGGGGCCTCCAGAACTCCAGGCGGTGTCTGTGCCTCAGCCTCTTCTCATTCCTGCTC
GTGGCGGGGGCCACCACGCTCTTCTGTCTACTGAACTTCGGGGTGATCGGTCCCAACAAG
GAGGAGAAGTTCCCAAATGGGCTCCCTCTCATCAGTTCCATGGCCCAGACCTCACACTC
AGATCATCTTCTCAAACTCGAGTGACAAGCCCGTAGCCACGTCGTAGCAAACCACCAA
GCAGAGGAGCAGCTGGAGTGGCTGAGCCAGCGTGCCAACGCCCTCCTGGCCAATGGCATG
GATCTCAAAGACAACCAACTGGTGGTACCAGCAGATGGGCTGTACCTTATCTACTCCCAG

18/23

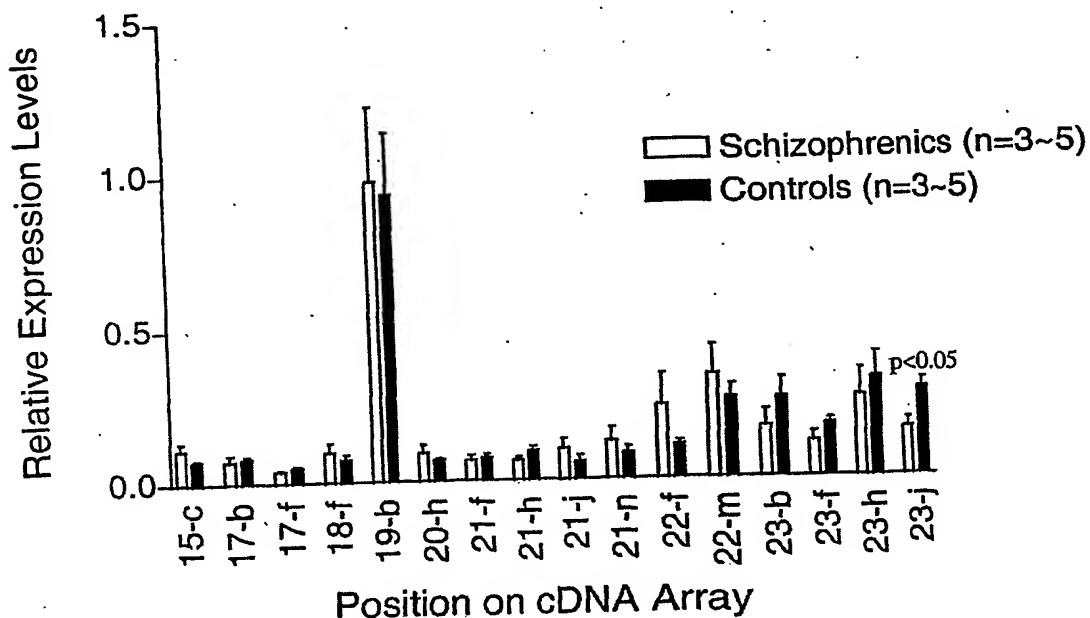
GTTCTCTTCAAGGGACAAGGCTGCCCCGACTATGTGCTCCTCACCCACACCGTCAGCCGA
 TTTGCCATTTTCATACCAGGAGAAAGTCAGCCTCCTCTCCGCCATCAAGAGCCCTTGCCCT
 AAGGACACCCCTGAGGGAGCTGAGCTCGAGCCCTGGTATGAGCCCATGTACCTGGGAGGA
 GTCTTCCAGCTGGAGAAGGGGGACCTGCTCAGCGCTGAGGTCAACCTGCCCAAGTACTTA
 GACATCACGGAGTCCGGGCAGGTCTACTTTGGAGTCATTGCTCTG

FIGURE 10b

Peptide sequence for YSG10 (SEQ ID No. 22) (TNF-alpha, rat)

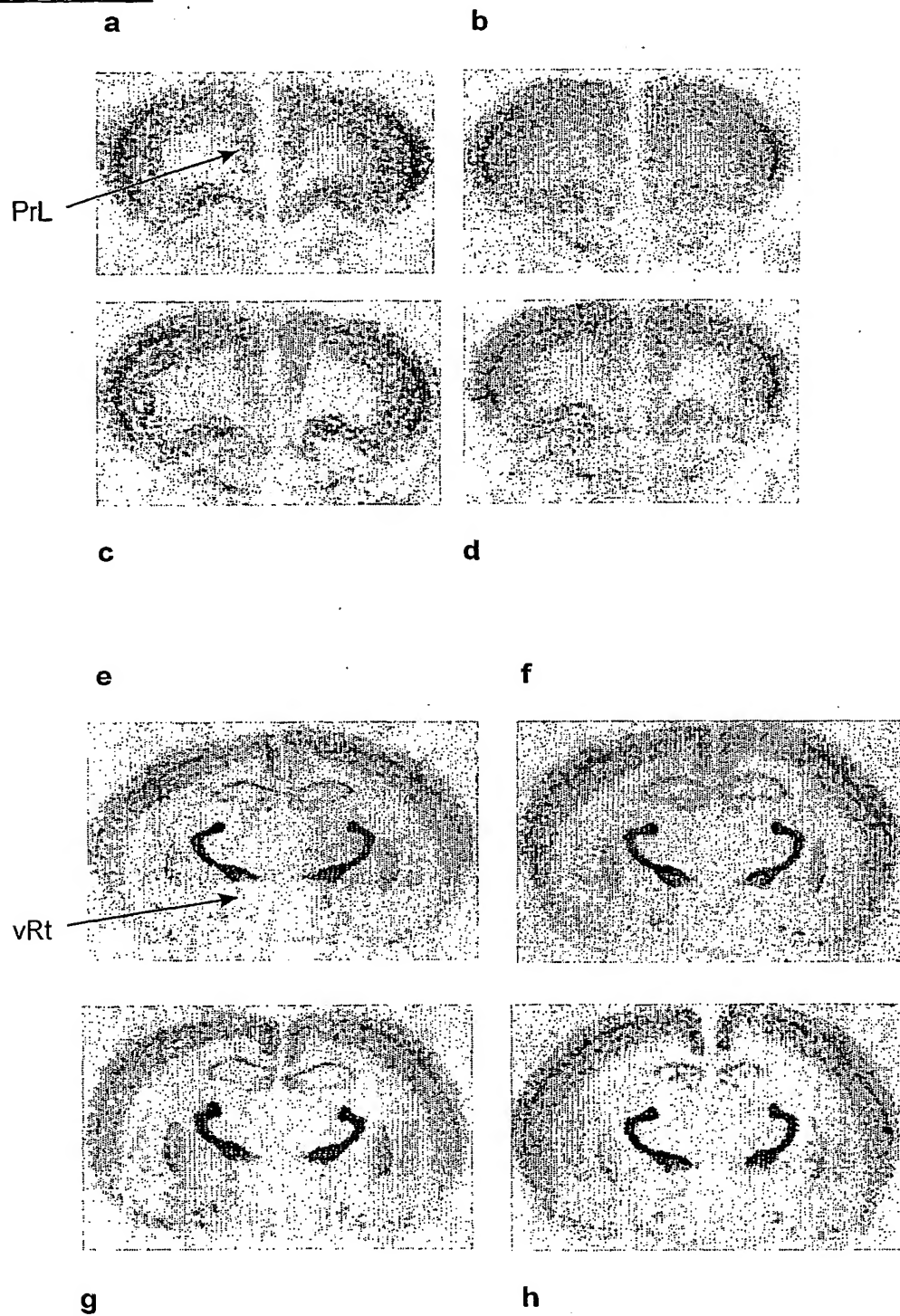
MSTESMIRDVELAEEALPKKMGGGLQNSRRCLCLSLFSFLLVAGATTFLCLLNFGVIGPNK
 EEKFPNGLPLISSMAQTLTLRSSSQNSSDKPVAHVVANHQAEQLEWLSQRANALLANGM
 DLKDNQLVVPADGLYLIYSQVLFKGQGPCDYVLLTHTVSRFAISYQEKVSLLSAIKSPCP
 KDTPEGAEKLPWYEPMYLGGVFQLEKGDLLSAEVNLPKYLDITESQVYFGVIAL

Figure 11



19/23

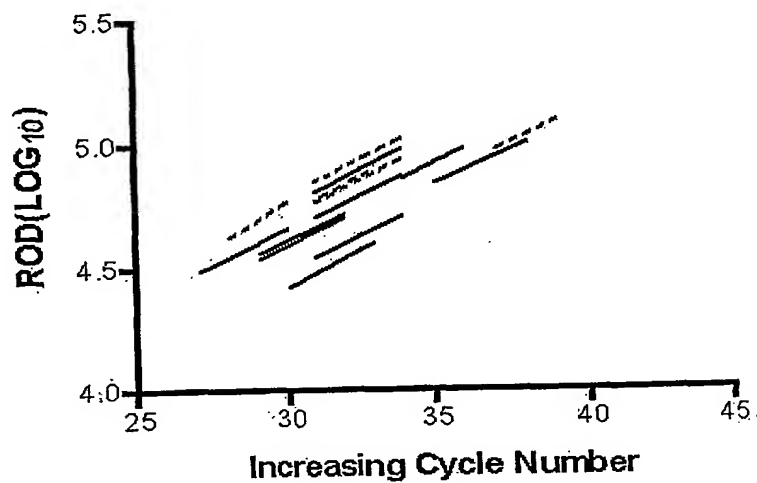
Figure 12



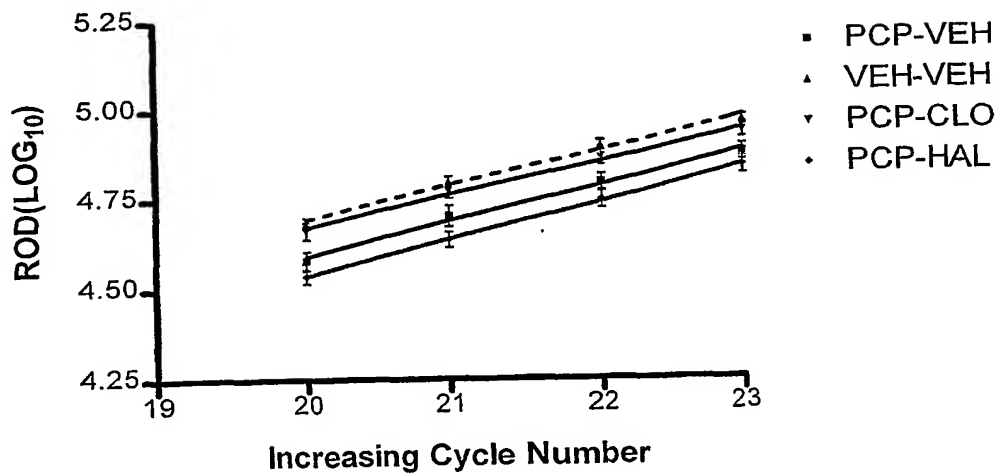
20/23

Figure 13

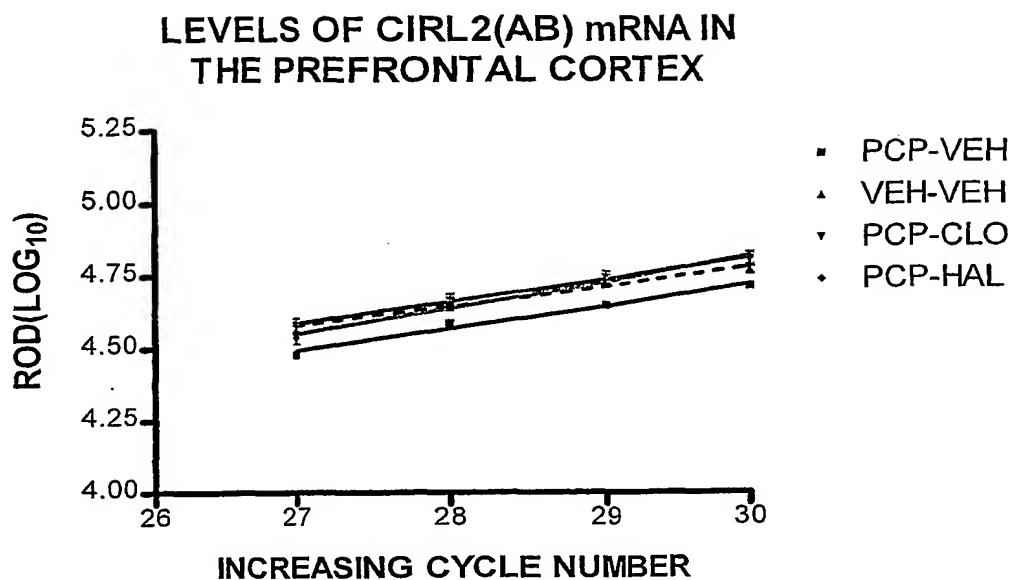
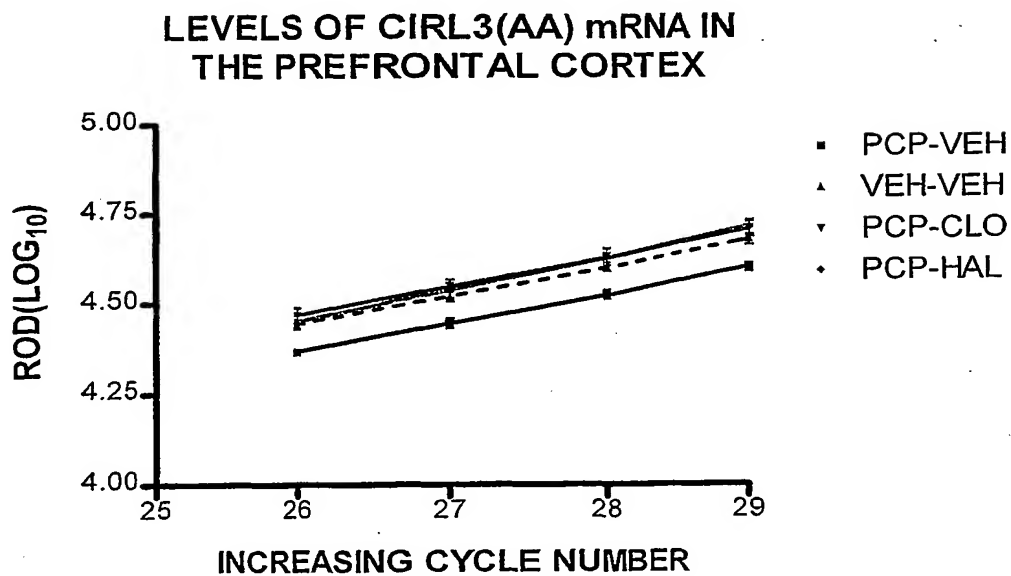
LEVELS OF CIRL1 mRNA IN
BRODEMAN AREA 11 FROM
HUMAN POST MORTEM BRAIN

Figure 14

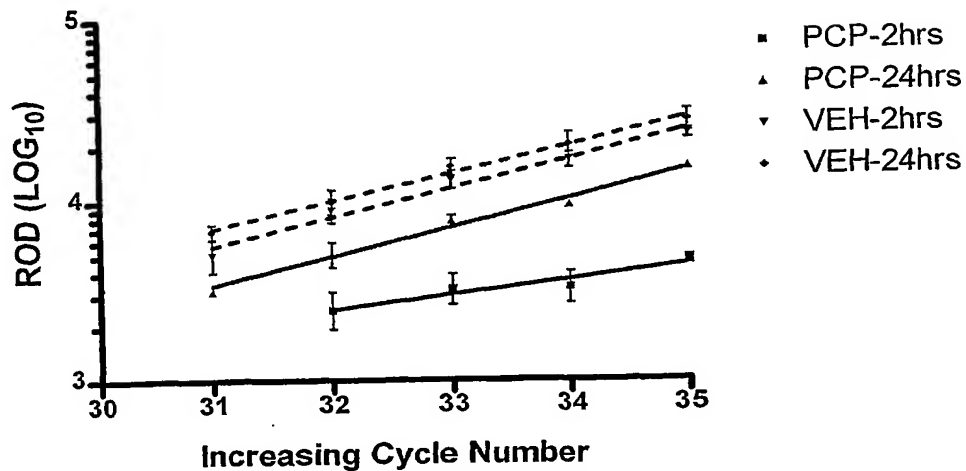
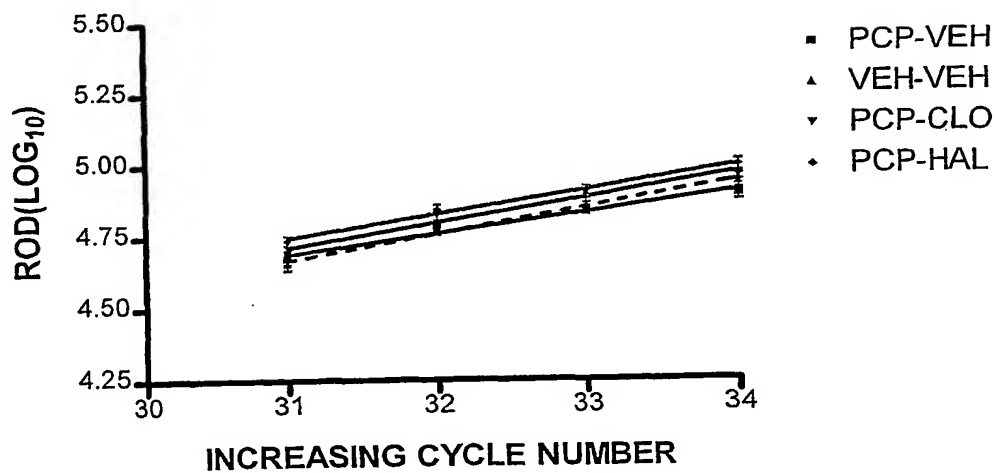
LEVELS OF CIRL1 mRNA IN
THE PREFRONTAL CORTEX



21/23

Figure 15Figure 16

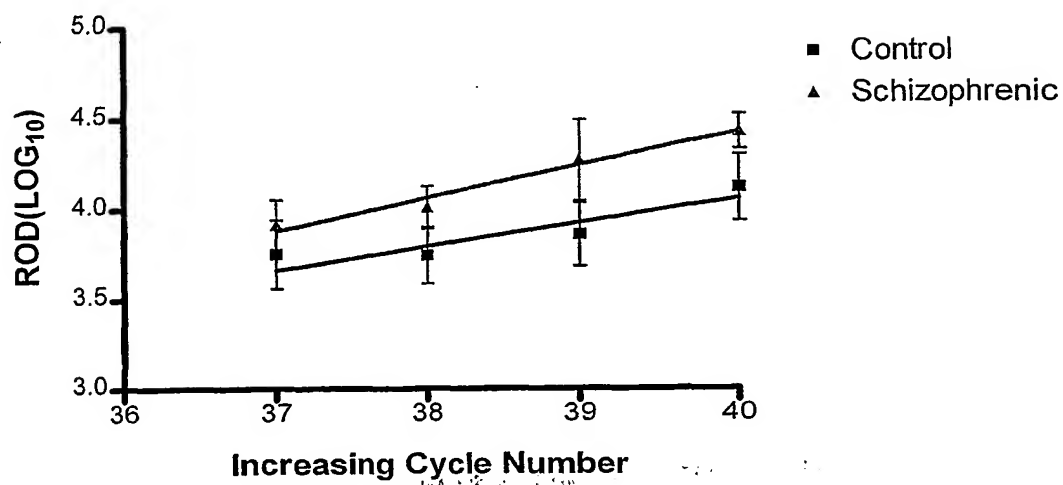
22/23

Figure 17**Effect of PCP Administration on
the Levels of $\text{TNF}\alpha$ in PFC**Figure 18**LEVELS OF $\text{TNF}\alpha$ mRNA IN
RAT PREFRONTAL CORTEX**

23/23

Figure 19

**Levels of $\text{TNF}\alpha$ mRNA in
Human Postmortem Orbital
Frontal Cortex**



THIS PAGE BLANK (USPTO)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
11 October 2001 (11.10.2001)

PCT

(10) International Publication Number
WO 01/075440 A3

(51) International Patent Classification⁷: **G01N 33/50**,
C12Q 1/68, C07K 14/47, C07H 21/04, C12N 15/63,
C07K 16/18, A61K 31/7088, C12N 5/10, A01K 67/027,
A61K 49/00

Glasgow G12 8QQ (GB). **PRATT, Judith** [GB/GB];
Yoshitomi Research Institute of Neuroscience in Glasgow
(YRING), West Medical Building, University of Glasgow,
Glasgow G12 8QQ (GB).

(21) International Application Number: PCT/GB01/01486

(74) Agents: **MCCALLUM, William, Potter et al.**; Cruik-
shank & Fairweather, 19 Royal Exchange Square, Glasgow
G1 3AE (GB).

(22) International Filing Date: 2 April 2001 (02.04.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0007880.8 31 March 2000 (31.03.2000) GB
0012768.8 26 May 2000 (26.05.2000) GB

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,
HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX,
MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL,
TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*): **MIT-
SUBISHI PHARMA CORPORATION** [JP/JP]; 2-6-9,
Hiranomachi, Chuo-ku, Osaka 541-0046 (JP).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **COCHRAN, Susan**
[GB/GB]; Welfide Corporation, 7-25. Koyata 3-Chome,
Iruma Saitama 358-0026 (JP). **PATERSON, Gary**
[GB/GB]; Yoshitomi Research Institute of Neuroscience in
Glasgow (YRING), West Medical Building, University of
Glasgow, Glasgow G12 8QQ (GB). **OHASHI, Yoshitaka**
[JP/JP]; Welfide Corporation, 7-25. Koyata 3-Chome,
Iruma Saitama 358-0026 (JP). **MORRIS, Brian** [GB/GB];
Yoshitomi Research Institute of Neuroscience in Glasgow
(YRING), West Medical Building, University of Glasgow,

Published:

— with international search report

(88) Date of publication of the international search report:
24 April 2003

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: SCHIZOPHRENIA RELATED GENES

(57) Abstract: There are provided isolated polynucleotide fragments for use in diagnosing and/or developing treatments for schizophrenia. Further provided is a method for diagnosing schizophrenia using one or more polynucleotides disclosed herein. Also provided is a method for screening a compound which regulates expression of a schizophrenia-related gene. Also provided is a chronic animal model of schizophrenia that mimics the functional deficits observed in patients and methods for producing the animal model comprising the administration of PCP to the animal.

WO 01/075440 A3

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 G01N33/50 C12Q1/68 C07K14/47 C07H21/04 C12N15/63
C07K16/18 A61K31/7088 C12N5/10 A01K67/027 A61K49/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12Q A01K G01N C07K C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EP0-Internal, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 39440 A (UNIV NEW YORK) 11 September 1998 (1998-09-11) claims 18,19 ---	1-34,45
A	WO 99 07739 A (UNIV ROCKEFELLER) 18 February 1999 (1999-02-18) claims 22-24 ---	1-34,45
E	EP 1 132 483 A (PRESIDENT OF NIIGATA UNIVERSITY) 12 September 2001 (2001-09-12) claim 1 --- -/--	1

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

27 June 2002

Date of mailing of the international search report

16. 09. 2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

OSBORNE, H

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JOHNSTON N ET AL: "Identification of differentially expressed messages in the hippocampi and frontal cortices of mentally ill individuals" SCHIZOPHRENIA RESEARCH, vol. 29, no. 1-2, 7 - 13 January 1998, pages 90-91, XP008004871 see abstract ---	1-34,45
A	QUI Y ET AL: "The use of DNA microarray to study genes affecting a phenotype related with schizophrenia in a mouse model" THE AMERICAN SOCIETY OF HUMAN GENETICS, vol. 65, no. 4, 19 - 23 October 1999, page AA417 XP002203420 see Abstract No 2359 ---	1-35
A	SHIMIZU E ET AL: "Glutamate dehydrogenase mRNA is immediately induced after phencyclidine treatment in the rat brain" SCHIZOPHRENIA RESEARCH, vol. 25, no. 3, 20 June 1997 (1997-06-20), pages 251-58, XP008004870 page 256, right-hand column, paragraph 1 ---	1-34,45
A	EDGAR P ET AL: "Comparative proteome analysis of hippocampus implicates chromosome 6q in schizophrenia" MOLECULAR PSYCHIATRY, vol. 5, no. 1, January 2000 (2000-01), pages 85-90, XP008004869 see Abstract -----	1-34,45

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-34, 45 all partially

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-34,45 all partially

Isolated gene sequences/gene products associated with schizophrenia; use of said sequences as indicators to diagnose schizophrenia, to monitor therapy, and to screen for drugs effective in treating schizophrenia, wherein the gene sequence(s)/gene product(s) relate to SEQ ID NO 1.

2. Claims: 1-34,45 all partially

Isolated gene sequences/gene products associated with schizophrenia; use of said sequences as indicators to diagnose schizophrenia, to monitor therapy, and to screen for drugs effective in treating schizophrenia, wherein the gene sequence(s)/gene product(s) relate to SEQ ID NO 2.

3. Claims: 1-34,45 all partially

Isolated gene sequences/gene products associated with schizophrenia; use of said sequences as indicators to diagnose schizophrenia, to monitor therapy, and to screen for drugs effective in treating schizophrenia, wherein the gene sequence(s)/gene product(s) relate to SEQ ID NO 3.

4. Claims: 1-34,45 all partially

Isolated gene sequences/gene products associated with schizophrenia; use of said sequences as indicators to diagnose schizophrenia, to monitor therapy, and to screen for drugs effective in treating schizophrenia, wherein the gene sequence(s)/gene product(s) relate to SEQ ID NO 4.

5. Claims: 1-6,20-34,45 all partially

Isolated gene sequences/gene products associated with schizophrenia; use of said sequences as indicators to diagnose schizophrenia, to monitor therapy, and to screen for drugs effective in treating schizophrenia, wherein the gene sequence(s)/gene product(s) relate to SEQ ID NO 5.

6. Claims: 1-6,20-34,45 all partially

Isolated gene sequences/gene products associated with schizophrenia; use of said sequences as indicators to diagnose schizophrenia, to monitor therapy, and to screen for drugs effective in treating schizophrenia, wherein the gene sequence(s)/gene product(s) relate to SEQ ID NO 7.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

7. Claims: 1-6,20-34,45 all partially

Isolated gene sequences/gene products associated with schizophrenia; use of said sequences as indicators to diagnose schizophrenia, to monitor therapy, and to screen for drugs effective in treating schizophrenia, wherein the gene sequence(s)/gene product(s) relate to SEQ ID NO 9.

8. Claims: 1-6,20-34,45 all partially

Isolated gene sequences/gene products associated with schizophrenia; use of said sequences as indicators to diagnose schizophrenia, to monitor therapy, and to screen for drugs effective in treating schizophrenia, wherein the gene sequence(s)/gene product(s) relate to SEQ ID NO 11.

9. Claims: 1-6,20-34,45 all partially

Isolated gene sequences/gene products associated with schizophrenia; use of said sequences as indicators to diagnose schizophrenia, to monitor therapy, and to screen for drugs effective in treating schizophrenia, wherein the gene sequence(s)/gene product(s) relate to SEQ ID NO 13.

10. Claims: 1-6,20-34,45 all partially

Isolated gene sequences/gene products associated with schizophrenia; use of said sequences as indicators to diagnose schizophrenia, to monitor therapy, and to screen for drugs effective in treating schizophrenia, wherein the gene sequence(s)/gene product(s) relate to SEQ ID NO 15.

11. Claims: 1-6,20-34,45 all partially

Isolated gene sequences/gene products associated with schizophrenia; use of said sequences as indicators to diagnose schizophrenia, to monitor therapy, and to screen for drugs effective in treating schizophrenia, wherein the gene sequence(s)/gene product(s) relate to SEQ ID NO 17.

12. Claims: 1-6,20-34,45 all partially

Isolated gene sequences/gene products associated with schizophrenia; use of said sequences as indicators to diagnose schizophrenia, to monitor therapy, and to screen for drugs effective in treating schizophrenia, wherein the gene sequence(s)/gene product(s) relate to SEQ ID NO 17.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

13. Claims: 1-6,20-34,45 all partially

Isolated gene sequences/gene products associated with schizophrenia; use of said sequences as indicators to diagnose schizophrenia, to monitor therapy, and to screen for drugs effective in treating schizophrenia, wherein the gene sequence(s)/gene product(s) relate to SEQ ID NO 19.

14. Claims: 1-6,20-34,45 all partially

Isolated gene sequences/gene products associated with schizophrenia; use of said sequences as indicators to diagnose schizophrenia, to monitor therapy, and to screen for drugs effective in treating schizophrenia, wherein the gene sequence(s)/gene product(s) relate to SEQ ID NO 21.

15. Claims: 35-44

A non-human animal for chronic schizophrenia and uses thereof in drug screening and diagnostic methods.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 01/01486

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 9839440	A	11-09-1998	AU	6685398 A	22-09-1998
			WO	9839440 A2	11-09-1998
WO 9907739	A	18-02-1999	US	6040168 A	21-03-2000
			US	2002064811 A1	30-05-2002
			AU	8772598 A	01-03-1999
			WO	9907739 A2	18-02-1999
EP 1132483	A	12-09-2001	JP	2001245661 A	11-09-2001
			EP	1132483 A2	12-09-2001